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THE MECHANISMS OF HEALING IN COLLAPSE THERAPY *

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THE results of collapse therapy, despite their spectacular improvement during the last decade, are often inconstant, unpredictable and disappointing. As culled from the literature the reasons for success or failure are manifold and often contradictory. On the other hand, a large number of clinical, pathological and experimental studies provides a sufficient basis for a discussion of the factors that play a beneficial or disturbing rôle in collapse therapy. While many single phases have been studied carefully, I failed to find in the literature a comprehensive discussion of the problem as a whole. A clear conception of the physiology of pulmonary collapse should obviously be the basis for correct therapeutic indications.

In this brief review it is impossible to discuss, with proper bibliographical documentation, the many divergent opinions on the subject. This will appear in a more extensive later publication. Within the time allotted for this presentation it is possible only to state briefly, and in rather categorical manner, what, on the basis of available knowledge, seems to be a justified idea of the mechanism of healing in pulmonary collapse. This is offered as a temporary working hypothesis which is necessarily far from complete. However, it has at least the virtue of clearing the field of a number of customary misconceptions.

Pulmonary collapse represents a reduced total volume of the lung. This may be induced by introducing foreign substances into the thoracic cavity (air, oil, paraffin, etc.), by paralyzing or cutting respiratory muscles (diaphragm, scaleni, intercostals), or by reducing the size of the bony thoracic cage.

When pulmonary collapse is established a number of compensatory mechanisms come into play; some of them operate immediately after collapse, others develop gradually and slowly. Many apparent contradictions in the literature are due to the fact that observations on brief acute experi-

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935.

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ments have been applied to therapeutic collapse which is always a chronic condition.

Another reason for confusion is the use of different species of experimental animals. Some species (guinea pigs, dogs) have a permeable mediastinum, so that any collapse measure (and particularly pneumothorax) instituted on one side causes bilateral collapse automatically, while other animals (rabbits, goats) have, like men, an impermeable mediastinum which, however, varies greatly in rigidity.

In the early era of pneumothorax therapy the aim was to immobilize the lung by superatmospheric intrapleural pressures. Later on it was found that subatmospheric intrapleural pressures yielded, in the majority of patients, equally good and better results than high positive pressures. At present, it ought to be, and probably is, common practice to maintain subatmospheric pressures unless stiff-walled cavities indicate the necessity of positive pressures for actual compression. But the logical explanation of the action of positive-pressure pneumothorax has been carried over insidiously and unjustifiably to subatmospheric pneumothorax and other collapse measures. This is a typical example of the lag that exists so often between practice and theory.

The following brief and necessarily incomplete list of the factors held responsible for enhancing healing under pulmonary collapse will indicate the chaotic state of the problem: (1) Rest of the collapsed lung, or part of it; (2) Elastic relaxation of pulmonary tissue; (3) Alteration of the circulation of the blood in the lung: hyperemia; blood stasis; relative anemia; (4) Alteration in the gaseous metabolism of the lung: anoxemia; increase in carbon dioxide; (5) Stasis of lymph; (6) Atelectasis: bronchial obstruction; (7) Cessation of spread in collapsed lung.

(1) *Rest of Collapsed Lung.* The respiratory motions of the lung are solely activated by the motion of the chest-wall (including the diaphragm). This is equally true for a normally expanded as well as for a collapsed lung. As long as any of the respiratory muscles perform their normal function so long is the lung ventilated. Even a large pneumothorax cannot alter the dependence of pulmonary motion upon thoracic motion up to the point where the intrapulmonary pressure is atmospheric or positive during the entire respiratory cycle. At this point ventilation must cease. According to Boyle's law, the expiratory increase of intrapleural pressure reduces a 1000 c.c. pneumothorax (at inspiration) only about 10 c.c. under the assumption that intrapleural respiratory amplitude between inspiration and expiration is equal to 10 cm. water; in other words, the compressibility of air introduces a practically insignificant lag between thoracic and pulmonary movement. Air introduced into the pleural cavity always causes two effects: (1) it reduces the volume of the lung; and (2) it expands the thoracic cage. The degree of the latter effect depends chiefly on the elastic properties of the chest wall and the mediastinum. Furthermore, when the total volume of the lung is decreased the residual air shows a greater percentage decrease than

does the vital capacity. If, as is usually the case, the collapsed lung contains lesions, the volume reduction of the diseased areas does not reduce the vital capacity. These three factors: expansion of the thoracic cage, reduction of residual air, and collapse of nonfunctioning parenchyma, combine to cause a reduction of the vital capacity after collapse which is considerably smaller than the amount of air inflated. For these reasons a collapsed lung *can* continue to be ventilated by the preoperative amount of air, and, even more, and by virtue of the close gearing of pulmonary and thoracic motions, the pneumothorax lung *must* continue to be ventilated, as long as the thorax moves and as long as the intrapulmonary pressure is not positive throughout the respiratory cycle.

These theoretical deductions are amply confirmed by spirographic measurements on patients and on experimental animals, by direct observations of collapsed lungs and by roentgenological studies.

Figures 1, 2 and 8 present roentgenological evidence of the respiratory motion of collapsed lungs.

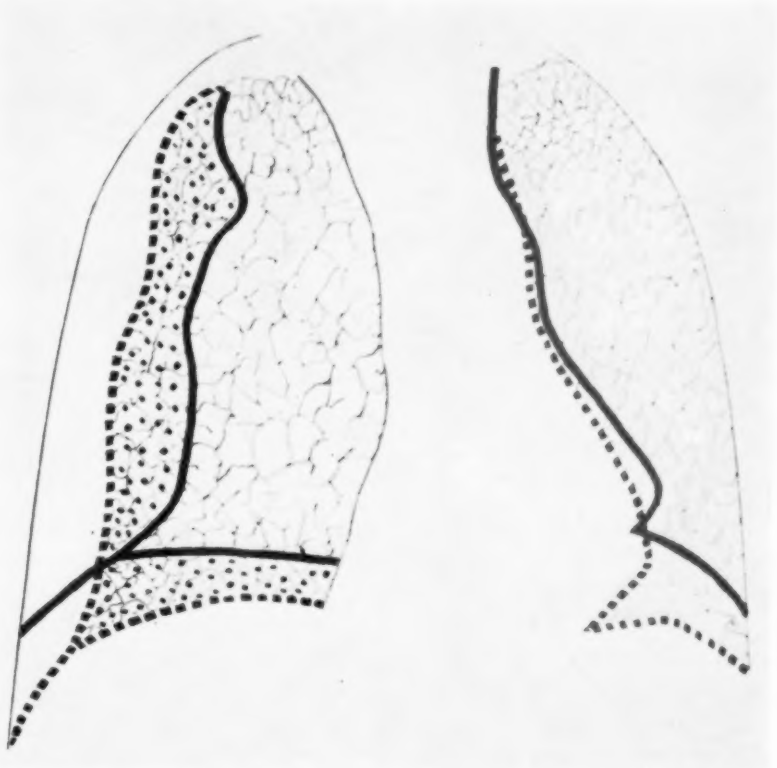
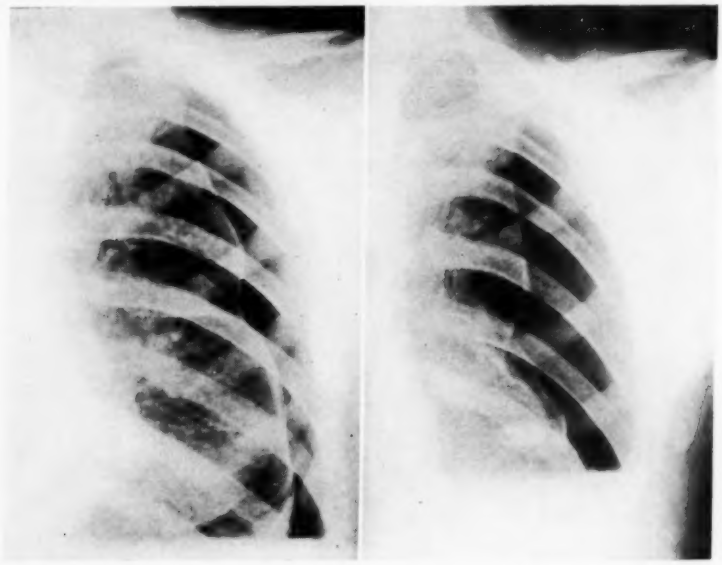


FIG. 1. Superimposed tracings of a pneumothorax lung in deepest inspiration and in deepest expiration to show the respiratory movement of the collapsed lung. The heavily dotted area shows the increase in size of the lung at inspiration over its size at expiration.
——: tracing at expiration
– – –: tracing at inspiration

Some limiting conditions must be mentioned. In the presence of an easily shifting mediastinum, the respiratory pressure changes cause a shifting of the mediastinum and a shifting of the lung *en bloc*, thus reducing the ventilation of the lung, as shown in figure 3.

When the diaphragm is paralyzed on the pneumothorax side, its paradoxical movement, activated by the intrapleural pressure changes, reduces the pulmonary ventilation. Paradoxical diaphragmatic movement occurs also in positive-pressure pneumothoraces without diaphragmatic paralysis. In positive pressure pneumothorax, if and when thoracic motion continues, the respiratory pressure changes cause only mediastinal shifting and paradoxical diaphragmatic motion, but no pulmonary ventilation.



a. *b.*

FIG. 2. Right lung, collapsed by pneumothorax: (*a*) in deepest inspiration, (*b*) in deepest expiration, to show the respiratory movement of the collapsed lung.

In order to find out how much a pneumothorax lung is ventilated, it is necessary to know the extent of mediastinal shifting, the degree of diaphragmatic paradoxical movement, and—last but not least—the amplitude of the thoracic (and diaphragmatic) movements. In uncomplicated pneumothoraces, the thoracic movements decrease but slightly. In the presence of pleural effusions and increasing fibrosis of the parietal pleura, thoracic movements are markedly reduced.

After proper consideration of all these factors it can be concluded that in subatmospheric pneumothoraces the collapsed lung continues to move. The incontrovertible proof of this statement is given by bilateral pneumothorax in which two collapsed lungs maintain normal gaseous exchange.

Regions of diseased pulmonary parenchyma, such as infiltrations, fibrosis,

a. *b.*

FIG. 3. Pneumothorax in the presence of a shifting mediastinum: (*a*) in deepest inspiration, (*b*) in deepest expiration. There is a marked shift of the mediastinal structures and of the right lung toward the left side during expiration. Mark that only the expiration film demonstrates the herniation of the mediastinum.

more or less fibrotic cavities, increase the normal elastic tension of the pulmonary tissue. When the pulmonary tissue relaxes, due to the reduction of the total volume of the lung, the parts under increased elastic tension will obviously retract more than the normal tissue. This is the basis of so-called selective collapse which is operative both in pneumothorax and, to a more limited degree, in diaphragmatic paralysis. In pneumothorax its manifestation is frequently prevented by adhesions inserted directly over the lesions. When selective collapse occurs, selective rest may occur as well. The less extensible, and hence more retracted, diseased portions are less easily expanded by the respiratory pressure changes; and in the ideal case they may be at complete * rest while the uninvolved tissue functions fully. This ideal case depends upon a delicate balance between the differential elastic tensions of normal and diseased tissue on the one side, and on the level and the amplitudes of the intrapleural pressure on the other side.

As far as other therapeutic collapse measures are concerned, similar considerations must be applied. In phrenicectomy, the piston action of the diaphragm is abolished, but costal motion continues, and is usually increased as a compensating mechanism. Hence, no functional rest can be expected from diaphragmatic paralysis. In an extensive thoracoplasty plus phrenicectomy, and in intercostal neurectomy, thoracic motion may become totally abolished, and then pulmonary rest is achieved; but this can be expected only in extensive and complete operations.

Summarizing the question of rest, it may be concluded that collapse may or may not establish mechanical rest for diseased parenchyma, that rest is frequently not procured in unquestionably successful procedures, and that therefore rest cannot be the sole, nor the dominant factor enhancing healing under collapse therapy.

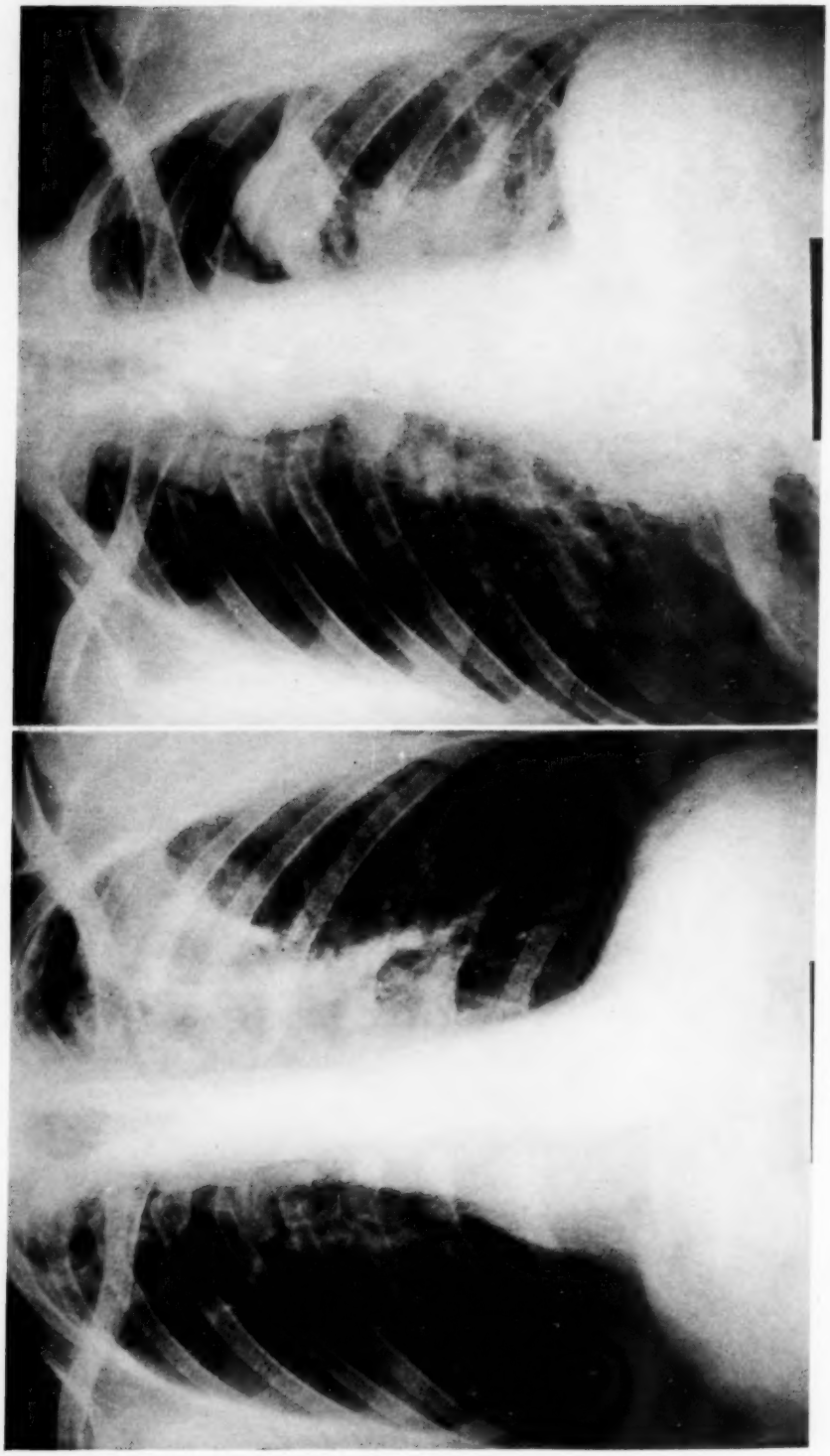
(2) *Elastic Relaxation.* Pulmonary collapse, i.e., reduction of total pulmonary volume, always causes elastic relaxation, regardless of the method by which collapse is induced. Relaxation diminishes or eliminates elastic tension which counteracts the natural shrinking tendency of scar tissue; it abolishes the traumatizing effect of the continuous strain on tissue under high elastic tension; and it allows cavity walls to approximate, thus establishing the mechanical prerequisite for spontaneous healing processes. The maximum elastic recoil occurs, unless prevented by adhesions, where the tissue is under highest elastic tension, that is, in the diseased portions of the lung. The pneumothorax lung assumes (in the absence of adhesions) the shape determined by its own differential elastic tensions, while the normally expanded lung is strictly dependent on the configuration of the thoracic cage. Pneumothorax liberates the lung as far as shape is concerned, but as far as motion is concerned it remains dependent on the thoracic cage within the limitation mentioned above.

The selective retraction of diseased portions of the lung in pneumothorax is clearly shown in figures 4 and 5.

* "Complete" is used here in a practical clinical sense. Strictly physically speaking absolute rest would be possible only if the diseased tissue were completely non-distensible.

a. *b*.

FIG. 4. (*a*) before pneumothorax; (*b*) eight months later, following bilateral pneumothorax. The upper portion of the right lung is selectively collapsed, the lower portion of the right lung is almost completely expanded. In the left upper region, selective collapse is prevented by adhesions.

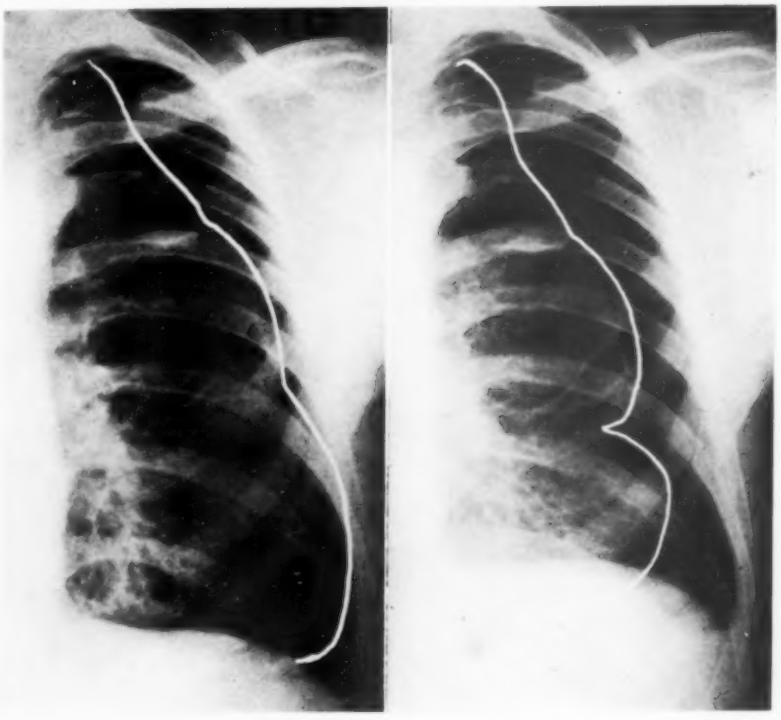


b.

a.

FIG. 5. (*a*) before pneumothorax; (*b*) five and a half months later, following bilateral pneumothorax. Well defined selective collapse of both upper lobes.

Elastic relaxation produces conditions obviously favorable for healing and it is a constant factor in all forms of collapse therapy. It seems justified; therefore, to regard elastic relaxation as an important, and probably the most important factor in enhancing healing under collapse therapy. It is therefore of greatest importance to assure it. In a pneumothorax, adhesions inserted over parenchymal lesions may completely prevent elastic relaxation, and exert an elastic strain whose inspiratory and expiratory variations may be greater than before collapse. The usual roentgenographs, taken at maximum inspiration, furnish often misleading and always inade-

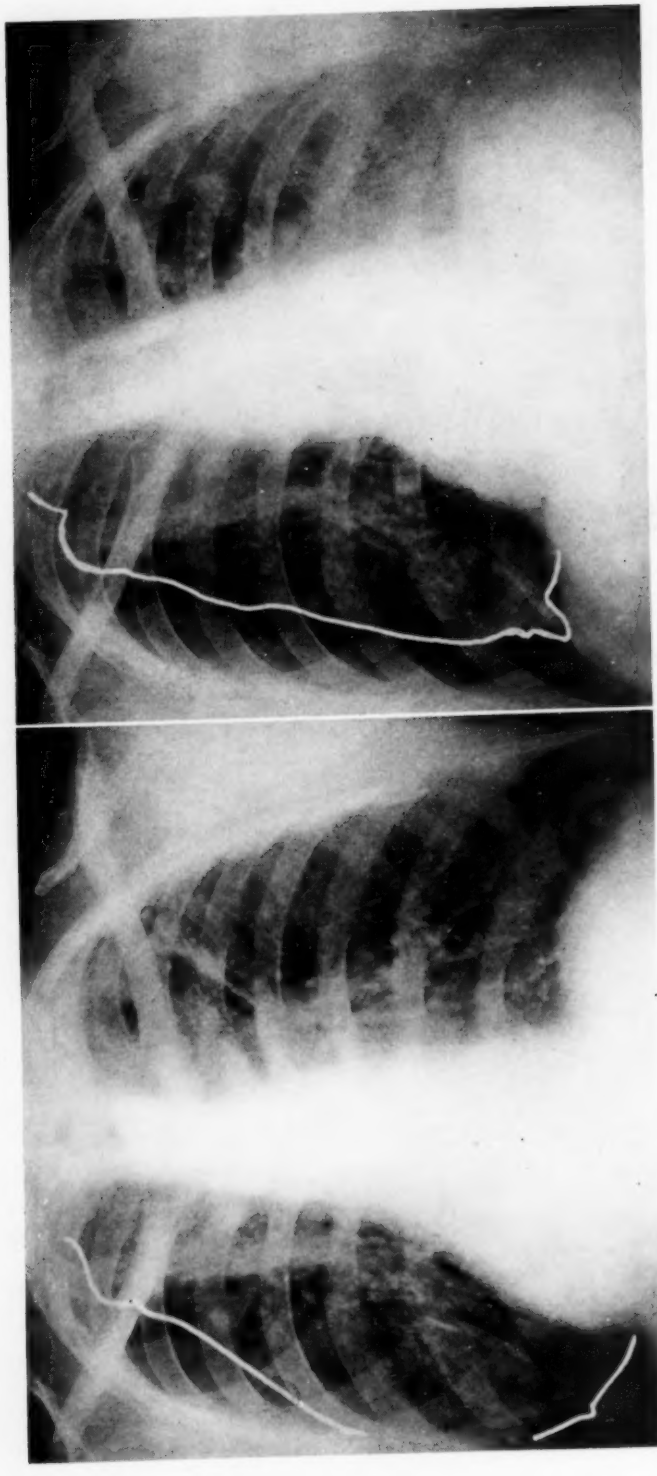


a. *b.*

FIG. 6. (*a*) deepest inspiration, (*b*) deepest expiration. These two roentgenograms show the marked difference in the *apparent* size of the pneumothorax cavity. The inspiration picture might wrongly suggest that the lower lobe is adherent to the chest wall.

quate information of the collapsed lung, because: (1) they show the intrapleural conditions in an unphysiological respiratory phase which the patient never assumes under natural conditions; and (2) they represent a static picture of the lung while interest should properly be centered on its dynamics.

Roentgenographs taken in maximum inspiration and in maximum expiration add significant information. While neither maximum inspiration, nor maximum expiration is a physiological phase, the normal respiratory cycle lies somewhere near the middle of these two extremes, and the direc-

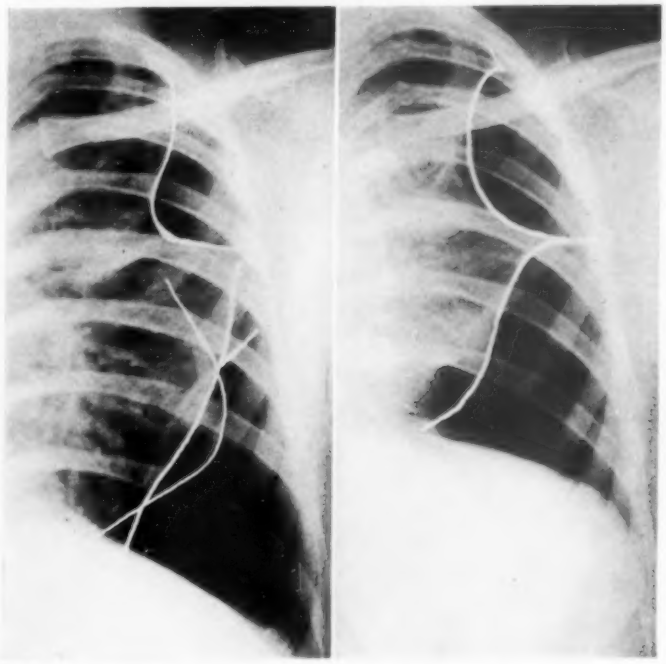


b.

a.

FIG. 7. (*a*) deepest inspiration; (*b*) deepest expiration. The inspiration picture shows a slight collapse of the left lung with the lower lobe touching the chest well and the mediastinal structures in normal position. The expiration film shows a moderate collapse of the entire left lung, the mediastinal structures markedly deviated to the right and a marked collapse of the right lung, particularly in its lower portion.

tion of forces operative in the chest is correctly shown. Inspiration and expiration films indicate roughly the actual degree of collapse (figure 6), the approximate degree of mediastinal shifting, the possible paradoxical movement of the diaphragm, the amount of contralateral collapse (figures 3 and 7), and—most important of all—they may demonstrate the presence of elastic strain produced by adhesions (figure 8). In addition to this, the expiration film shows, after small initial inflations, much more clearly the presence of a pneumothorax (figure 9.) The comparison of the two films makes possible an approximate estimation of the degree of antero-



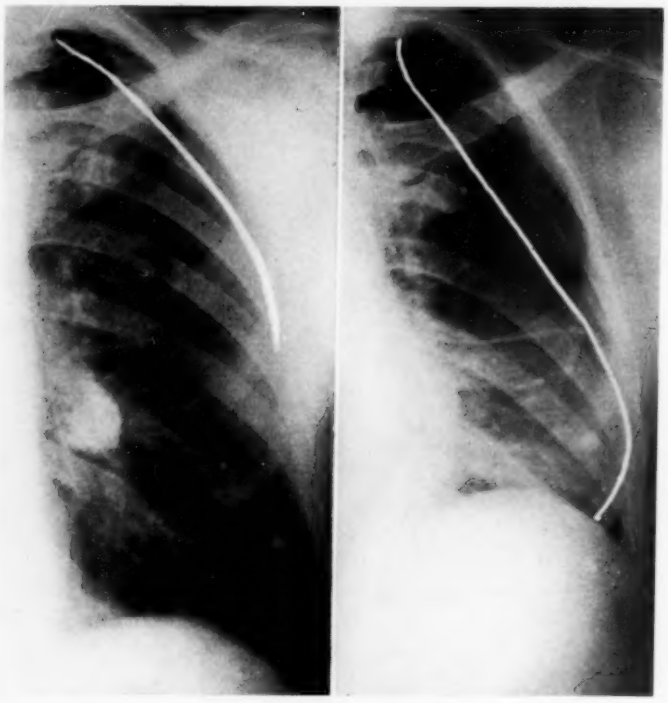
a. *b.*

FIG. 8. (*a*) deepest inspiration; (*b*) deepest expiration. The expiration film shows clearly the marked pull which the adhesion in the third anterior interspace exerts on the lung. The respiratory movement of the collapsed lung is clearly shown, not only by its increase in volume but by its greater transparency in inspiration.

posterior collapse. Inspiration-expiration films, properly interpreted, yield incomparably more information than a set of stereo-films taken at inspiration.

(*3*) *Hyperemia, Blood Stasis, Relative Anemia.* The changes that collapse causes in the blood circulation of the lung are the subject of numerous discussions and of extensive experimental and pathological studies. Without entering here into a lengthy discussion of the subject it should be emphasized that this problem is exceedingly complex and the technical and methodological difficulties of its experimental approach are well realized.

The Fick principle of estimating the blood flow is limited in its application because, by this method, only the fully aerated portion of the blood is measured, thus making it impossible to ascertain that amount that may flow through nonventilated portions of the lung. However, it is important to remember that it seems fairly well established that in uncomplicated pulmonary collapse the arterial blood is, as a rule, normally oxygenated. Since, as was pointed out, collapsed lungs may be ventilated by a normal, a larger, or a smaller than normal, amount of air, it appears very suggestive—and consistent with observational data—to think that a parallelism exists between



a. *b.*

FIG. 9. (*a*) deepest inspiration; (*b*) deepest expiration. These roentgenograms show how much more easily a small pneumothorax is visualized in expiration than in inspiration.

ventilation and circulation. This is confirmed by direct experimental observations on normal animals which indicate that the pulmonary blood flow increases during inspiration and decreases during expiration. If the above assumption is correct it is obviously impossible to make a categorical statement about hyperemia or anemia in a collapsed lung since either condition may prevail, depending on the state of ventilation. In collapsed lungs of long standing—the only ones that are of therapeutic interest—ventilation is probably decreased as a rule; hence relative anemia should be expected, and this seems to be the usual postmortem finding. Whether such anemia, when

it exists, has a definite therapeutic effect is undecided; it has been suggested that it may stimulate fibrosis.

(*4*) *Anoxemia; Increase in Carbon Dioxide.* These two factors are claimed to be of great therapeutic significance by producing a gaseous milieu unsuitable for the life of the tubercle bacillus. It is well established, however, that the tubercle bacillus, although a strict aërobic organism, continues to grow " until the last atom of oxygen is consumed," and is not inhibited by atmospheres containing 10 to 50 per cent of carbon dioxide. Obviously it is impossible that bactericidal degrees of anoxemia or of carbon dioxide concentrations exist in a collapsed lung. Even lesser degrees would be inconsistent with normal oxygenation of arterial blood in collapse therapy. While it is possible that minor degrees of anoxemia and of carbon dioxide increase may be less favorable for the activity of the tubercle bacillus than the normal gaseous tension in the lung, these changes—if and when they exist—can play only a minor therapeutic rôle.

(*5*) *Stasis of Lymph.* Experimental evidence is convincing, though not entirely undisputed, that the lymph flow is slower in a collapsed than in a normally expanded lung. This fact may largely explain the beneficial influence that collapse so often exerts on toxic symptoms. By virtue of the slower lymph flow, toxic products are considerably more diluted in the blood stream than before collapse. It is probable, too, that lymph stasis exerts a stimulating effect on fibrosis; morphological observations show that fibrosis develops in diseased and collapsed lungs particularly in the perilymphatic tissue.

(*6*) *Atelectasis; Bronchial Obstruction.* Atelectasis, according to strict medical usage, though not according to etymology, means complete airlessness of pulmonary tissue. Incomplete atelectasis is therefore a *contradictio in adjecto* and this term should not be used. Uncomplicated collapse with subatmospheric pressure never leads to atelectasis. Atelectasis cannot be produced by external pressure on the lung but only by bronchial obstruction with subsequent absorption of the alveolar air, or by its functional analogue: a non-ventilated lung (positive pressure pneumothorax, otherwise completely immobilized lung). Bronchial obstruction, according to postmortem observation, is extremely rare in lungs collapsed on account of tuberculosis. Bronchial stenosis or obstruction, particularly if a bronchus draining a cavity is affected, is, as a rule, a grave complication with all the alarming symptomatology and the potentially perilous developments due to retention of secretion. It is therefore most unlikely that bronchial obstruction is—as has recently been claimed—the major healing mechanism of cavities and other tuberculous lesions in the lung. Pathological evidence for the therapeutic effect of bronchial obstruction is lacking. Furthermore, it would appear that the clinical and roentgenological diagnosis of atelectasis, which appears so frequently in the recent literature, is usually poorly substantiated. Due to the mechanism of collateral respiration, the obstruction of a small

bronchus does not lead to atelectasis so that the diagnosis of so-called lobular atelectasis rests on most uncertain ground. It is fully consistent with this view that foci healed by fibrosis in a collapsed lung are regularly surrounded by non-atelectatic, and frequently by emphysematous parenchyma.

When atelectasis does occur it does not *per se* cause fibrosis as is often assumed. So-called collapse-induration is not the result of simple atelectasis, but of atelectasis plus inflammation. If uncomplicated atelectasis would cause fibrosis one would expect to find, following complete thoracoplasties, that the whole lung would be fibrosed. The usual finding is, however, that the tuberculous lesions are fibrosed, and that the intervening parenchyma is not.

(*7*) *Cessation of Spread in Collapsed Lung.* Evidence of hematogenous spread in collapsed lungs, even in cases of generalized miliary tuberculosis, is very rare. The same thing is true of lymphatic and, to a lesser degree, of bronchogenic spread. These phenomena are not well understood. The reduction of the lymph and blood stream in a collapsed lung must be important factors. The tortuous course of bronchi in a collapsed lung and under certain conditions, the diminished momentum of the air stream, may cause the diminution of bronchogenic propagation.

In many particulars, knowledge of the physiological effect of pulmonary collapse is incomplete and understanding is unsatisfactory. To mention one practical and outstanding example: there is no convincing explanation of the fact that collapse seems to enhance resorption of exudative infiltrations. It is hoped that the recently revived pneumothorax treatment of lobar pneumonia may furnish observations not only to confirm, but also to explain this fact.

Summary

In the healing of tuberculous lesions under collapse therapy, the following factors—roughly in order of their importance—seem to be operative:

1. Elastic relaxation diminishes or eliminates elastic strain on diseased tissue, thus enhancing scar contraction and closure of cavities.

2. Relative, and in some cases absolute rest of foci of disease is produced by the mechanism of selective collapse, by splinting or immobilizing the thoracic cage, or by procedures enforcing localized relaxation and immobilization.

3. Actual compression (positive pressure pneumothorax) helps to collapse stiff-walled cavities and to stretch adhesions.

4. Tortuosity of bronchi and the slowing of the air stream in a collapsed lung help to diminish bronchogenic spread.

5. The slowing of the blood and lymph stream prevents hematogenous and lymphatic propagation. Diminution of the lymph stream may reduce toxemia.

6. It is possible, but not proved, that relative anemia and lymph stasis may stimulate fibrosis.

7. A reduction of the oxygen tension and increase in the carbon dioxide tension in the pulmonary tissue may possibly produce conditions that are somewhat less favorable for the life of the tubercle bacillus.

I wish to express my thanks to Dr. C. A. Thomas and Dr. S. C. Davis for their permission to use in this paper clinical and roentgenological material from the Southern Pacific Hospital in Tucson.

LYMPHEDEMA OF THE EXTREMITIES: ETIOLOGY, CLASSIFICATION AND TREATMENT; REPORT OF 300 CASES *

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General information about lymphedema tends to be somewhat confused and vague. This situation is largely the result of the relative rarity of the condition; of an inadequate knowledge of its etiology, bacteriology, and pathology, and of the lack of a comprehensive classification. Although it is impossible to rectify all these shortcomings, we feel that a presentation of the pertinent data from the records of 300 cases observed at The Mayo Clinic in the previous 10 years offers an opportunity to fill some of the gaps in knowledge. To this end, we are describing the condition, offering a clinical classification, and presenting what is known regarding etiology, diagnosis, and treatment. Aids to such a presentation are furnished by recent excellent work on the anatomy and physiology of lymph and lymph vessels, well illustrated by the work of Drinker and Field. These facts regarding the anatomy and physiology of lymph vessels and lymph are so important for an understanding of lymphedema that it seems advisable to review them briefly.

Definition of Terms

Lymph is a fluid obtained from lymph vessels. Tissue fluid is found in the region outside of the blood and lymph capillaries in the cellular interspace. Plasma is the unclotted fluid of the blood. Lymphedema is a swelling of soft tissues which is the result of an increased quantity of lymph. Elephantiasis has been defined as a "progressive histopathologic state characterized by a chronic inflammatory fibromatosis or hypertrophy of the hypodermal and dermal connective tissue," [21] but the term has been used loosely to apply to a variety of conditions which produce enlargement of the extremities. We suggest, therefore, discontinuation of use of this term, which adds confusion to medical terminology.

Anatomy

Lymph vessels either are modified veins or arise in situ from mesenchymal cells. They are closed vessels which possess an unbroken endothelial lining, bathed on the outside by tissue fluid. In general, there is more lymphatic than hematic capillary surface. Every main blood vessel has an accompanying lymph vessel.[25] The lymph vessels are as richly supplied

* Read at the Philadelphia meeting of the American College of Physicians, May 2, 1935.

From The Mayo Clinic, Rochester, Minnesota.

with valves as are the veins.[5] India ink injected between two ligatures into the lumen of an artery appears in the lymph vessels around the artery by passing through intracellular stomas and directly through the cells of the arterial wall.[17]

There are a superficial and a deep system of lymph vessels in the leg, but there is no communication between them except through the popliteal and inguinal lymph nodes.[30] In animals most of the superficial lymph vessels of the leg and foot, as well as some of the deep lymph vessels that drain the muscles of the leg, terminate in the popliteal lymph node. From this node large efferent trunks course along the femoral vessels to end in the external iliac nodes, just distal to the bifurcation of the aorta. Many of the superficial lymph vessels of the thigh and upper part of the leg drain into the inguinal lymph nodes, which in turn have efferent vessels terminating in the external iliac nodes. The deeper lymph vessels in the muscle sheaths of the thigh eventually enter trunks that accompany the main femoral lymph vessels, and drain into the large iliac nodes.[27] All the lymph vessels of the leg, both superficial and deep, join at the groin and pass along the external and common iliac vessels through the iliac nodes. The lymphatic trunks at the root of the leg hug the veins closely, and may even be embedded in the adventitia of their walls. They are enclosed in a tough fibrous sheath along with the great blood vessels.[12]

The superficial lymph vessels of the third, fourth and fifth fingers pass to the dorsum of the digits, then upward and around the ulnar side of the forearm to the flexor side of the forearm, where they join those coming from the entire ulnar side of the forearm and pass upward into the axillary nodes, with or without intervention of the cubital lymph node. Those of the index finger and thumb pass upward on the dorsum of these digits, then around the radial side of the forearm to the flexor surface, where they join those coming from the radial side of the forearm, and pass upward to the axillary nodes. An occasional lymph vessel may pass upward on the extensor surface of the forearm to well above the elbow, where it turns sharply around the ulnar side of the arm to its inner side and thence to the axillary nodes. The superficial lymph vessels of the arm empty into the axillary nodes or, much less frequently, into the deltoidopectoral or supraclavicular nodes. The deep lymph vessels of the arm run with the large vessels to empty into the axillary lymph nodes, with or without the intervention of the deep cubital lymph nodes. The superficial and deep lymph vessels are connected at the elbow by the deep and superficial cubital lymph nodes.[3]

Regeneration and Collateral Circulation. If a large lymph vessel is cut, the circulation is carried on by collateral vessels. Later, the passage between the two cut ends regenerates, and the collateral circulation recedes. Collateral lymph vessels develop a few days after ligation of the main trunks.[6] Regeneration of lymph vessels is rapid. They cross the scar of

an incision as early as the fourth day, and by the eighth day regeneration is physiologically adequate.[26]

Physiology

The endothelium of the lymph vessels is more permeable than that of blood capillaries. It does not possess any selective absorptive power, but merely admits material that is forced on its outer surface. Particles of microscopic dimensions which are deposited in various parts of the body, cannot move far except by entering and passing along the lymph vessels.

Pressure and Circulation of Peripheral Lymph. Active or passive contraction of skeletal muscles plays the most important part in the movement of lymph of man; the valves of the lymph vessels serve as the most important accessory arrangement for moving lymph forward.[5]

The circulation of lymph is rapid, but it varies greatly. Trypan blue that is injected into the lymph vessel of the foot of a dog may reach the receptaculum chyli in 10 seconds, and sodium salicylate that is injected similarly can be detected in the lymph of the thoracic duct in one minute and 20 seconds. Bromphenol blue, when injected intravenously, appears in the cervical lymph in two and a half minutes.

The pressure of lymph varies considerably, depending on the animal studied and the situation at which the pressure is determined. Ordinarily, it is only equivalent to a few millimeters of water. It is greatly increased by exercise and inflammation.

Coagulation of Lymph. Lymph contains fibrinogen and prothrombin, but it clots more slowly (from 10 to 20 minutes) than blood (from four to six minutes), owing to deficiency of thromboplastic substance ordinarily supplied in a large degree by blood platelets that are absent in lymph. This deficiency is corrected and coagulation of lymph occurs whenever cells in contact with the lymph stream undergo necrosis, or whenever lymph stasis and living bacteria in lymph coexist.[24] When thrombosis of the lymph vessels occurs, the thrombi contract and shrink away from the wall of the vessel, leaving adequate space for the circulation of lymph, except when the coagulating process is progressive. Lymph vessels may be completely filled with thrombi in the region of a phlegmon.

Various foreign substances injected into an area of severe inflammation do not pass into the lymphatic capillaries, but the same substances, when injected intravenously, accumulate rapidly in the inflamed area. Both observations are explained on the basis of thrombosis of the lymph vessels and the presence of a fine network of fibrin which obstructs the flow of lymph away from the inflamed area.*

Experimental Studies of Lymphedema

Complete excision of the iliac and inguinal lymph nodes of animals does not produce lymphedema which, however, can be produced temporarily by

* Unless a specific reference has been given in the preceding paragraphs, the authority is the monograph of Drinker and Field.[4]

dividing the limb of a dog transversely, leaving only the carefully denuded femoral artery and vein, and by suturing the edges of the wound.[26]

The rôle that lymphatic occlusion plays in phlegmasia alba dolens, which ordinarily has been considered to be the result of venous thrombosis, has

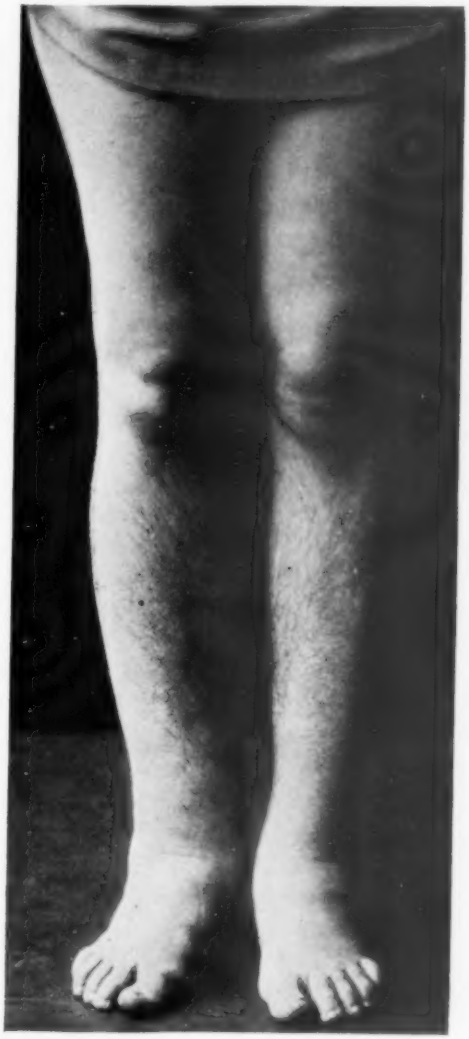

FIG. 1. Lymphedema precox affecting a woman aged 18 years. At the age of 13 years there was sudden swelling of the right leg and two years later the left leg became swollen.

been studied experimentally by Homans; Homans and Zollinger, and Zimmermann and de Takáts. Homans believed that experimental and clinical phlegmasia alba dolens was caused, in a large degree, by lymphatic obstruction, but Zimmermann and de Takáts could not find support for this view, with their experiments.

The problem of the production of chronic lymphedema of animals had not been solved until recently when Homans, Drinker, and Field reported the reproduction of characteristic lymphedema in dogs by injecting a solution of quinine and a suspension of silica into lymph vessels in several areas, which produced a thrombosis of these vessels. A steadily increasing content of protein was noted in the lymph; the deep layers of the skin and subcutaneous tissues steadily became the sites of an increasing fibrosis which was evidence of active proliferation of connective tissue. Attacks of acute lymphangitis, which produced fever and prostration, occurred spontaneously. Hemolytic streptococci could be recovered from the edematous tissue at the beginning of the attacks but never at any other time. When thorotrast was injected into the edematous legs, the direction in which it flowed depended entirely on gravity; it ran toward the foot just as well as away from it, through capacious valveless series of pond-like and river-like lymph vessels.

Etiology of Lymphedema of Man

Lymphedema, which affects human beings, appears to have a multiple etiology. The mechanism of its production which is, however, apparently the same in all cases, is predicated on clinical and experimental observations. Lymph stasis occurs primarily as a result of obstruction that is produced by inflammatory or noninflammatory processes, or by lymphangiectasis, which occurs in association with congenital lymphedema. When obstruction occurs, the intralymphatic pressure increases, and causes dilatation of lymph vessels with subsequent insufficiency of the valves, forcing lymph to seek new channels which are supplied inadequately with valves. Since valves are very important in causing the lymph to move centrally, incompetence of the valves causes further stasis of lymph. The protein content of the lymph increases and fibroblasts proliferate rapidly since the lymph is an excellent culture medium for the growth of fibroblasts. This fibrosis contributes further to lymph stasis. As a result of the increased quantity of lymph in the tissues, attacks of acute inflammation may recur, producing thrombosis of lymph vessels, more stasis of lymph, and, hence, more fibrosis. The cycle, which is a vicious one, consists of stasis of lymph, fibrosis, inflammation with further stasis, and, hence, more fibrosis.

Pathology

Excellent studies of lymphedematous tissues are available. Unfortunately, specific findings have not been correlated with the particular type of the disease, or with the phase of the disease at the time the tissue was secured for study. Perhaps this correlation is not possible but this should be determined. While morphologic studies have determined the basis of enlargement of the limb in cases of lymphedema, they have shed but little light on etiology. It is to be hoped that the experimental production of lymphedema will lead to orderly presentation of the morphologic changes

which occur as minimal lymphedema progresses to marked lymphedema and hypertrophy of the limb. Our studies, which are incomplete, indicate that the morphologic changes, which are present in cases of congenital lymphedema, are characteristic of this condition.[20] The subcutaneous tissue is increased in thickness and the adipose tissue is replaced by enlarged lymph spaces and by connective tissue. Thrombosis of lymph vessels and of blood

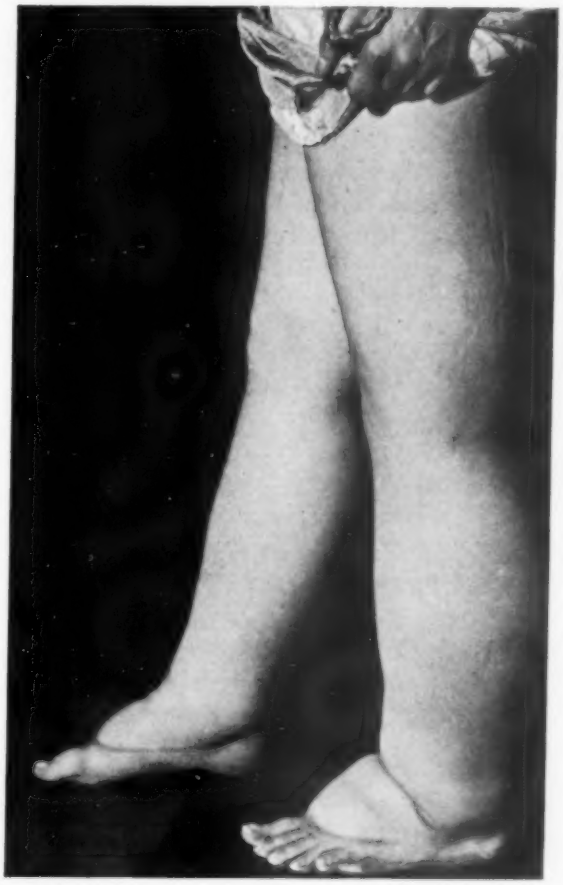

FIG. 2. Lymphedema precox with secondary cellulitis affecting a woman aged 23 years. The right leg had swelled at the age of 10 years. When the patient was 20 years old, acute cellulitis and lymphangitis had involved both legs following which both legs had remained swollen.

vessels, and evidence of inflammation are routinely absent. Pathologic changes reported in various types of lymphedema are variable. Thickening of the skin and subcutis; replacement of adipose tissue by enlarged lymph spaces and by connective tissue; atrophy of muscle, nerve fibers, and sweat glands; infiltration of most cells, especially lymphocytes and leukocytes; and a variety of other changes, have been described.[7, 28, 31]

Classification of Lymphedema of the Extremities of Man [1]

The cases of lymphedema studied lend themselves to division into two main groups, inflammatory and noninflammatory; the terms infectious and noninfectious could be used as well. The division into the two groups indicates the original state; lymphedema which is originally noninflammatory may be complicated eventually by inflammatory changes. Most cases of lymphedema may be classified without difficulty according to the tabulation. The classification is purely clinical.

Noninflammatory Lymphedema

Primary Lymphedema. "Lymphedema precox" is an original term applied to a definite clinical syndrome manifested in 93 cases in the group studied. It affected female patients predominantly (87 per cent of the cases), and in the majority of instances (65 per cent) had its onset between the ages of 10 and 24 years, inclusively. The term "precox" is used here

Classification of 300 Cases of Lymphedema

	Cases
A. Noninflammatory	
I. Primary	
Precox	93
Congenital	
1. Simple	12
2. Familial (Milroy's disease)	0
II. Secondary	
Malignant occlusion	32
Surgical removal of lymph nodes	61
Pressure	1
Roentgen and radium therapy	3
B. Inflammatory	
I. Primary (single or recurrent acute and chronic)	41
II. Secondary (single or recurrent acute and chronic)	
Venous stasis	13
Trichophytosis	5
Systemic diseases	5
Local tissue injury or inflammation	33
Filariasis	1

to denote an early development; in many of the cases in this group the onset of symptoms occurred at puberty, and the incidence of onset in adolescence was impressive.

The swelling occurs spontaneously and without known cause; at the onset, the patient ordinarily notices a puffiness about the foot or ankle. The edema is worse during long periods of activity, during the menses and in warm weather. Rest in bed and elevation of the extremity produce temporary disappearance of the edema that may affect one lower extremity exclusively (70 per cent in this series) or both legs simultaneously, or one extremity may swell months or years after the opposite member has become involved.

The edema ordinarily progresses up the leg slowly, and eventually the entire limb becomes edematous over a period of months or years. The

spread of the edema may, however, be much more rapid; the entire limb may be involved within a few days or weeks. In many instances, swelling is limited to the foot and ankle or does not extend above the knee. Frequently, this particular state is doubtless merely a phase of a progressive condition, but in other instances it seems to represent the maximal degree of extension of the edema.

Gradually the swelling, whatever its limitations, becomes more marked; elevation and rest in bed cause its reduction but not its disappearance. The smooth skin becomes roughened, and the hitherto soft edema becomes resistant to pressure. In addition to enlargement of the limb due to edema, there is actual hypertrophy of tissue, and the limb becomes unsightly, ungainly and uncomfortable. A dull, heavy sensation is present, but there is no actual pain.

The entire course of the swelling is ordinarily one of smooth progression; acute lymphangitis and cellulitis occur infrequently (in 13 per cent of the cases studied). Ulceration of the skin does not occur. The entire history is ordinarily that of conversion of a normal limb into a swollen one; nothing else is noteworthy.

The cause of lymphedema precox is obscure. The predominant incidence among female patients, the onset in the majority of cases during adolescence and the accentuation during menstruation tend to indicate that the reproductive organs play a part in the condition. Possibly the additional load thrown on the lymph vessels by rapidly developing reproductive structures induces a functional incompetence of the lymph vessels or allows entrance of infection into the lymph trunks and nodes in the pelvis. Even minor degrees of functional inadequacy, through obstruction in the pelvis, might lead to dilatation of the lymph vessels below, with incompetence of the valves, particularly among women, whose subcutaneous tissues offer little support. The resulting interference with the free passage of tissue fluid into the lymph vessels provides adequate encouragement for the growth of fibroblasts and further obstruction by connective tissue. Homans, Drinker, and Field reported a case in which the lymphedema apparently was of the precox type. At exploration, greatly enlarged lymph vessels were found in the pelvis; this was an indication of obstruction proximally.[13] It is possible that the entire explanation rests on a congenital underdevelopment of lymph vessels, or their inability to develop quickly enough to supply adequately tissues that are growing rapidly. Limitation of the disease to the lower extremities is striking, and it indicates that gravity is an important factor in the development.

Congenital Lymphedema. This may be either simple or familial. In both types, lymphedematous swelling, usually of one lower extremity, is present at birth. There may be actual hypertrophy of the limb which is the result of fibrous hypertrophy. In other instances, the skin is soft, and the edema is less resistant to pressure. The two forms do not vary, except that in the simple type blood relatives are not similarly affected. In the

familial type, several persons in the same family have lymphedematous swellings of one or more extremities. The familial type, known as Milroy's disease, was first described by him as a clinical entity in 1892. Milroy said:

"Briefly stated, chronic hereditary edema consists in a firm edema. It is limited in extent to the toes or a part or the whole of one or both feet, or

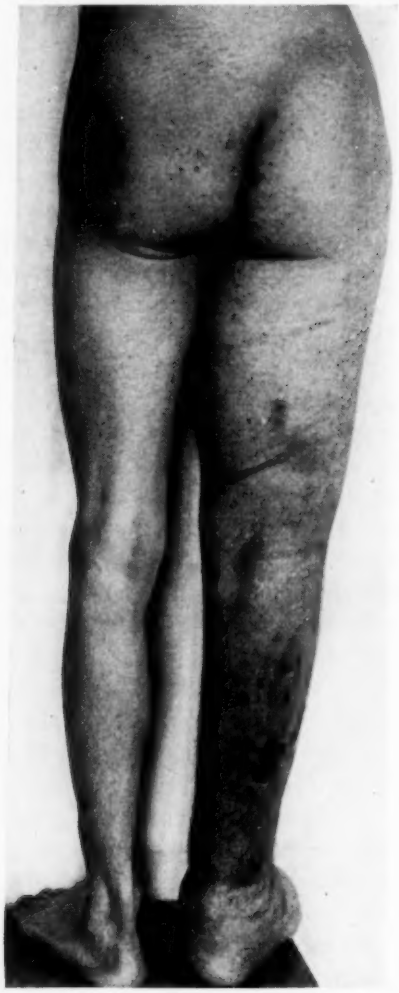

FIG. 3. Congenital lymphedema of the right leg affecting a boy 16 years old.

of one or both legs. It never extends above Poupart's ligament. It is not painful or tender and is without constitutional symptoms. It arises from no apparent cause. Hereditary transmission is conspicuous in its behaviour." [16]

Milroy's original report was based on a study of six generations of a family of 97 persons, of whom 22 had lymphedema; 21 of the 22 having

been born with the condition. Variations from the criteria of Milroy have been so great that the term "Milroy's disease" as used concurrently, is largely without significance. Meige found only eight cases in four generations; the onset at puberty was striking. Under the title Milroy's disease, Hope and French reported 13 instances of this disease among 42 persons in five generations [15]; in no instance was the condition congenital; the time of onset ranged from infancy to manhood, and attacks of recurrent cellulitis and lymphangitis occurred. Familial lipodystrophy is apparently confused with Milroy's disease. There were no instances of Milroy's disease in our series of cases. Occasionally, a patient said that he or she believed that a relative was similarly affected with swelling of the extremities, but the details were vague, and in no instance was it proved that the lymphedema was both congenital and familial.

That the criteria of Milroy have been departed from is to be deprecated. Familial lymphedema is not Milroy's disease, according to Milroy's definition, unless the condition is congenital. Many of the cases called "Milroy's disease" are doubtless examples of lymphedema precox with a familial predilection. The marked hereditary and congenital features, which were present in Milroy's cases, have not been equaled in cases that have been reported by others. The situation that was recorded by Milroy may be unique. This constitutes further reason for close adherence to the diagnostic criteria that have been given. Recent pathologic studies of tissues which have been removed from patients who had congenital lymphedema, show that widely dilated lymph spaces and connective tissue occupy the space ordinarily taken up by subcutaneous tissue.[20] The original lesion is apparently lymphangiectasis, a congenital malformation or one which was acquired in intra-uterine life. Lymph stasis results and fibrosis occurs.

Secondary Lymphedema. This may be the result of malignant occlusion of lymph vessels by metastasis of malignant disease of the breast, uterine cervix, uterus, vulva, prostate gland, bladder, testes, skin, or bones to adjacent lymph nodes. Such a possibility serves to emphasize the necessity of close scrutiny for evidence of malignant disease in all cases of lymphedema, since swelling may be the first outward manifestation. Pressure outside the lymphatic trunks perhaps occasionally, but rarely, produces lymphedema. The one case of lymphedema apparently due to pressure in this series seemed to follow the use of a truss for inguinal hernia. Secondary, noninflammatory lymphedema may occur in cases of Hodgkin's disease, or lymphosarcoma, or it may be associated with multiple hemorrhagic sarcoma, which has been described by Kaposi [18]; or it may follow surgical removal of lymph nodes and lymph vessels for malignant disease distally situated, or for tuberculosis or metastasis of malignant disease. The last named condition is the elephantiasis chirurgica of Halsted. Such a condition is not uncommonly seen following radical amputation of the breast and the removal of the axillary lymph nodes for carcinoma. The lymphedema may occur with or without intercurrent attacks of lymph-

angitis and cellulitis. The irregular interval at which lymphedema occurs after radical amputation of the breast is remarkable. Usually, the arm begins to swell on resumption of activity, but weeks, months, or even years, may pass before the extremity becomes edematous. In one instance, the arm was free from swelling for nine and a half years; there was no evidence of the recurrence of malignancy to account for the edema; and cellulitis

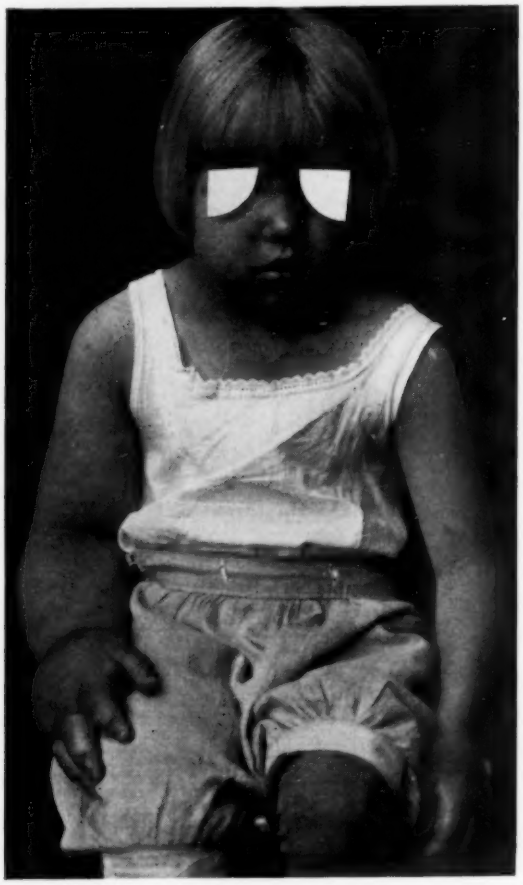

FIG. 4. Congenital lymphedema of the right arm and right side of the face, affecting a girl four years old.

and lymphangitis had not occurred. In such instances, it is possible that fibrosis may be induced by repeated irradiation, thus producing lymphatic obstruction, or that occult lymphedema, which has been present for years, has resulted in overgrowth of connective tissue and obvious edema. Unfortunately, there are no experimental data to explain the occurrence of edema after radical removal of the breast; experiments on animals reveal that extensive removal of lymph nodes does not cause edema. Why, then,

does this condition occur in man after extensive removal of lymph nodes? Halsted believed it was caused by infection following operation, either obvious or so slight as to avoid detection, or by recurrent attacks of cellulitis and lymphangitis. The question cannot be answered here. The answer may be inherent in the comparatively small number of experiments performed for the removal of lymph nodes of animals; lymphedema has not been demonstrated with these experiments, but neither does it occur in many instances following radical removal of the breast of a human being. If larger numbers of animals were observed over greater periods of time following surgical removal of lymph nodes, it is probable that lymphedema would be noted. The conclusion based on clinical observation cannot be avoided; surgical removal of, or metastasis to, lymph nodes may produce lymphedema.

Lymphedema may occur after treatment with radium and roentgen-rays. Whether such a result is brought about by the fibrosis caused by irradiation, or by metastasis of the malignant disease for which radiation is given, cannot be determined with certainty. Barker described a case in which radium irradiation for a disease, apparently incorrectly diagnosed as carcinoma of the uterine cervix, was followed by lymphedema.

Inflammatory Lymphedema

General characteristics: The advanced stage of inflammatory lymphedema has been called "elephantiasis nostras streptogenes." All examples of inflammatory lymphedema, exclusive of the chronic form, have one feature in common, single or recurrent attacks of acute cellulitis and lymphangitis. The contrast between lymphedema of inflammatory origin and of the precox type is striking; in the former, progression is by a series of attacks which are impressive in the suddenness of onset, and striking in the severity of systemic reaction; in the latter, the history is one of slowly progressive edema. The usual victim of an attack of cellulitis and lymphangitis of an advanced grade is suddenly seized with a severe chill unpreceded by other symptoms, or, following a short period of distress in the extremity or in its proximal lymph nodes, his teeth chatter, the bed shakes and he becomes nauseated and vomits. His temperature is between 101 and 106° F.; in a short time a small, reddened area spreads until a considerable portion of the extremity is swollen, red, hot and tender. The proximal lymph nodes are tender and swollen. The chills recur during a period of 30 minutes to an hour. The high fever persists for a period ranging from a few hours to two or three days, and is accompanied by marked malaise that may persist after the temperature returns to normal. The abnormal condition of the extremity recedes slowly over a period of from four to 14 days but, after all clinical signs of acute inflammation have disappeared, swelling is present in a greater degree than before the attack. The organism chiefly responsible for the attacks of acute inflammation is the streptococcus.[2]

Single attacks leave minor degrees of lymphedema, but successive attacks, which tend to occur progressively, more frequently produce increasing edema; each attack is a step toward the final stage, namely, marked lymphedema. The chronic form of lymphangitis of the spontaneous type is exceedingly rare. In such instances, the leg is persistently warmer than its companion member, and a reddish discoloration of the skin exists. In many instances, lymphedema following injury or infection develops without the intervention of acute attacks of lymphangitis and cellulitis or of clinical manifestations of chronic lymphangitis. The infection in such instances is considered to be subclinical. It should be emphasized that lymphangitis, whatever its nature, produces occlusion of lymph vessels by thrombosis which produces lymph stasis which in turn provokes further fibrosis and more stasis of lymph.

Primary Lymphedema. This term signifies a condition resulting from single or recurring acute attacks or from chronic lymphangitis and cellulitis not secondary to any known local abnormality, such as venous or lymphatic stasis or extraneous infection. In many such instances, the lymphangitis appears to occur in much the same spontaneous manner as tonsillitis or phlebitis. In other instances, it may be due to infections introduced into the lymph vessels through minor portals of entry unnoticed by the patient. The acute attacks of lymphangitis and cellulitis have been described; each attack leaves a residue of increased edema. In the chronic form of lymphangitis, the edema is slowly progressive.

Secondary Lymphedema. This term indicates a condition resulting from lymphangitis secondary to known causes. The lymphangitis may occur in single or recurrent attacks or in a chronic form. Chronic edema of venous origin may predispose to recurrent attacks of acute cellulitis and lymphangitis, and thus to progressive lymphedema, but such instances are uncommon, in light of the rather common occurrence of thrombophlebitis resulting in edema.

Trichophytosis about the toes may induce recurrent attacks of acute lymphangitis. The inflammation and the resultant edema are ordinarily limited to the foot and ankle. It is probable that an etiologic relationship exists in but a small percentage of instances in which trichophytosis and acute attacks of lymphangitis occur in the same patient. It is not clear whether the trichophytes themselves or secondary bacterial invaders are responsible, even when the trichophytic infection seems to be definitely related to the acute inflammatory attacks. Instances which strongly suggest that the Trichophyton is directly or indirectly responsible for the acute attacks are those in which marked evidence of trichophytic infections, such as desquamation and the occurrence of vesicles, precede the appearance of cellulitis and lymphangitis. Pregnancy and systemic diseases, such as influenza, typhoid fever, pneumonia, malaria, and filariasis, may lead to recurrent attacks of cellulitis and lymphangitis, and result in lymphedema. Except in cases of filariasis, it is possible that the original lesion is a thrombo-

phlebitis that produces lymphatic as well as venous occlusion, as shown by Homans,[11] and thus subsequent attacks of lymphangitis and, eventually, clinical lymphedema. Occasionally, conversion into the lymphedematous state proceeds without the intervention of attacks of acute inflammation; in such instances, it is assumed that a condition of chronic lymphangitis exists, or that the lymph vessels become obstructed by overgrowth of connective tissue which is, in turn, a reaction to stasis of tissue fluid. Tissue fluid acts as an excellent culture medium; fibroblasts grow and fibrosis

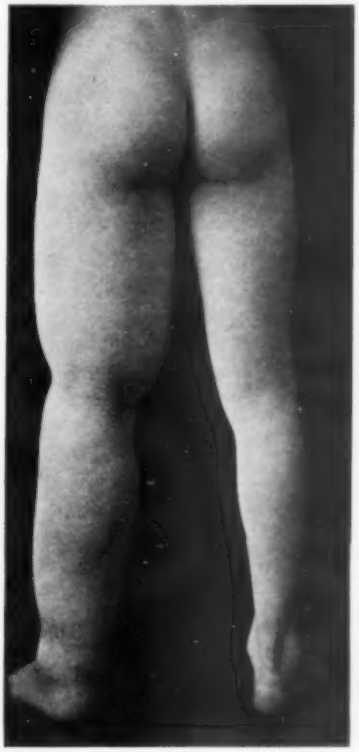

FIG. 5. Secondary inflammatory lymphedema affecting a boy, aged 16 years. At the age of 13 years a "boil" appeared on the inner side of the left thigh, followed by swelling of the entire leg.

results unless the blood plasma is promptly returned to tubes lined with endothelium. It is worthy of note that filariasis was not demonstrated in any of the cases of lymphedema reported in this study. Clinical evidence of, or an antecedent history suggestive of, filariasis was present in but one case. A physician who had observed many cases of lymphedema caused by Filaria, in China, examined this patient and expressed the opinion that the condition was characteristically one of lymphedema caused by Filaria. An acute episode of inflammation did not occur while the patient was under our observation, and Filaria were not demonstrated in the blood; in many

instances, blood drawn from other patients at night was studied, but Filaria were never found. It is possible, if not probable, that filariasis existed in some of the cases reported, for it has been shown that failure to find Filaria does not exclude filariasis. The patients of The Mayo Clinic are drawn largely from northern climates where filariasis exists sporadically, if at all, and it is obvious that the absence of this condition as a cause of lymphedema would not hold in more southern locations where filariasis is common.

Local inflammation or injury of tissue most commonly leads to the production of lymphedema through the intermediation of single or recurrent attacks of lymphangitis or chronic lymphangitis. In the cases studied, such diverse causes as contusions, lacerations, surgical incisions, vesicles, abscesses, furuncles, burns, fractures, penetrating wounds, bites by dogs, tularemic abscesses, pelvic inflammatory diseases, and appendicitis were directly responsible. The acute attacks may occur weeks or months after the original trauma, which may not be associated with any marked clinical evidence of infection. Some stasis of lymph, subclinical in degree or unnoted by the patient, seems to exist; then, for some unknown reason, marked bacterial activity occurs, and an acute attack of cellulitis and lymphangitis is clinically apparent. It seems strange that minor abrasions should allow entrance of infection into the tissues, but Hudack and McMaster demonstrated that the slightest wound of the corium may tear lymph vessels open and permit material to enter them directly. In many instances, the lymphedema occurred following injury or infection without the intervention of acute attacks of inflammation, and seemed to be caused by chronic or subclinical inflammation and thrombosis of lymph vessels, or by minimal lymph stasis which provoked connective tissue overgrowth.

Differential Diagnosis

There is rarely any difficulty in distinguishing advanced lymphedema from other types of edema. The brawny indurated skin and the hypertrophied limb of advanced lymphedema bear little resemblance to manifestations of edema in other diseases. It is only when the lymphedema is not associated with changes in the appearance and feel of the skin that difficulty arises. Lymphedema can be distinguished without difficulty from the edema of general systemic diseases, such as myxedema, myocardial failure, nephrosis, nephritis or deficient proteinemia, when it is unilateral; when it is bilateral, a thorough examination is necessary to exclude these diseases. Sarcomas, lipomas, and neoplasms of the bone are almost uniformly unilateral, and they produce regional or localized swellings, whereas the edema of lymphatic obstruction is more uniform and extensive. When swelling of an extremity is localized, careful roentgenologic studies are invaluable from a diagnostic standpoint. Angioneurotic and cyclic edemas are characterized by intermittence, whereas lymphedema is more constant and disappears during the early phase only on elevation of the limb; well ad-

vanced lymphedema responds to this procedure incompletely. Enlargement of a limb in arteriovenous fistula is associated with dilatation of and increased pressure in the regional veins; analysis of the blood from these veins reveals an oxygen content approaching that of arterial blood. If the arteriovenous fistula is congenital, or was acquired before longitudinal growth of the bones ceased spontaneously, the limb is increased in length as well as in circumference. All these signs of arteriovenous fistula, except the increased circumference of the limb, are absent in lymphedema.

The edema of limbs occasionally noted in lymphosarcoma is probably of

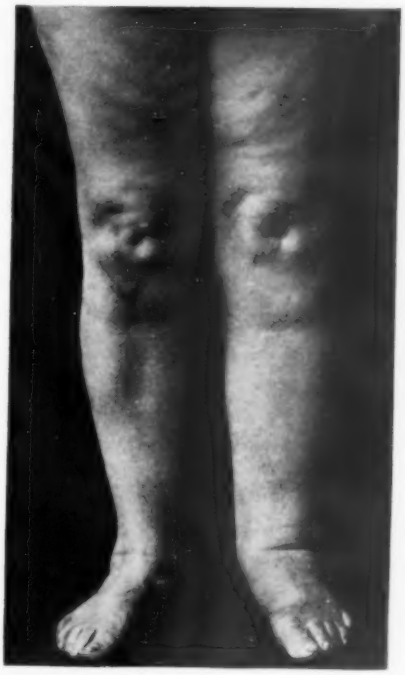

FIG. 6. Secondary inflammatory lymphedema associated with trichophytosis, affecting a woman, aged 55 years. A vesicular, itching lesion of the skin of the toes, and of the dorsal and plantar surfaces of the left foot, had been present for four years. Attacks of acute lymphangitis and cellulitis recurred, and edema had been present for three and a half years. At the time of examination, trichophytes were found in the cutaneous lesions.

lymphatic origin, but recognition of the basic condition is important. Ordinarily, in cases of lymphosarcoma, there are enlarged nodes in the regions in which nodes are usually palpable, and in the mediastinum. Microscopic examination of a node removed surgically is invaluable when doubt exists. It may be remarked parenthetically that it is always important to examine patients with lymphedema carefully for evidence of malignancy.

Lipodystrophy, characterized by " fat legs," is to be distinguished from lymphedema. The characteristic symptoms which lymphedema and lipodystrophy may have in common are predilection for women, similarity in

appearance, painlessness and additional swelling of the feet or ankles when patients are much on their feet, particularly in warm weather. Lipodystrophy is uniformly bilateral, and is usually associated with generalized obesity or obesity about the pelvis. The degree, but not the extent, of lipodystrophy may progress after it is first noted. In contrast, lymphedema is usually unilateral, is not ordinarily associated with obesity and usually progresses from the foot proximally, except when it is congenital. Attacks of lymphangitis and cellulitis may occur in lymphedema but not in lipodystrophy. Pitting on pressure may occur in both conditions, but it is less evident in lipodystrophy. The diminution in size, which may follow elevation of the extremities in both conditions, is more marked in lymphedema.

The edema of deep thrombophlebitis is usually to be distinguished from lymphedema because the former is similar to lymphedema in so many respects. Well advanced stages of either condition offer little difficulty in diagnosis. The hypertrophied limb, with the thickened skin and firm consistency, characteristic of advanced lymphedema, has little similarity to the limb in cases of deep thrombophlebitis, for the latter is marked by softer edema, stasis ulcers, dermatitis and superficial varices. To be sure, when attacks of recurrent lymphangitis or cellulitis occur, the leg that was originally edematous from venous obstruction acquires an additional element of lymphedema, and lymphedema may occur around varicose ulcers as a result of chronic infection. So far as we are aware, however, pure uncomplicated lymphedema, whatever its origin, does not lead to ulceration. It is in the earlier phases of the two diseases that difficulty is encountered; the usual similarity of symptoms includes unilaterality, pitting on pressure, normal skin texture and disappearance of edema following elevation of the limb. Dissimilarities exist in the circumstances of origin, speed of onset and progress, distress experienced by the patient and condition of the superficial veins. Thrombophlebitis with edema usually occurs in the course of or following an illness such as pneumonia or typhoid fever, or follows childbirth or operation. During the acute stage, a dull aching distress occurs in the area of the involved vein, which is tender to pressure; the edema develops rapidly to its fullest extent in the course of hours, and the superficial veins are dilated and the pressure within them is increased. Lymphedema does not ordinarily occur during systemic disease. The absence of distress is striking, except when acute cellulitis and lymphangitis occur; the edema ordinarily develops to its fullest extent slowly during a period of weeks, months, or years, and the superficial veins are not dilated. Among dissimilarities, the localized distress that occurs in thrombophlebitis is most important. Occasionally, the two conditions may coexist, as in the case of the thrombophlebitic limb that is involved in recurrent attacks of lymphangitis and cellulitis. In rare instances, it may be difficult, if not impossible, to distinguish between the two conditions, although roentgenologic studies

may be of some value.[26] The difficulty is particularly great when patients can relate only vague details about the development of the edema. Further study of the disappearance of dyes injected into edematous tissues, and of the renal excretion of dyes in such experiments may aid in the differential diagnosis.

Medical Treatment

Medical treatment, in order to be of value, must be carried out early. There is no medical treatment of value when the limb is greatly hypertrophied from the overgrowth of connective tissue. Treatment must be instituted when the edema first becomes evident. The longer uncontrolled lymphedema exists, the more fibrosis occurs, and the less efficient medical treatment becomes. This point needs to be emphasized, for most of our patients who have lymphedema have had it for a long time, and marked fibrosis, which cannot be influenced by medical treatment, has already occurred.

Control of Edema. The rationale of attempting to control edema is based on a conception of the condition within the tissues. Large lymphatic spaces exist, valves are absent or are functionless as a result of dilation of the lymph vessels, and lymph, which ordinarily moves proximally as a result of muscular activity and the action of valves, is static, or flows to dependent parts. A close parallelism exists with the condition present in varicose veins. The problem is one of causing the lymph to move toward the body by preventing stasis. We know of no way to accomplish this medically, other than by compressing the limb by adequate bandaging. An important first step is elevation of the extremity until as much as possible of the lymph has been removed from the extremity. Cloth bandages are of little or no value; the support which they give is of little value. Elastic stockings are unsatisfactory in many instances, for the same reason; they tend to stretch and lose their elasticity. Adhesive bandages are somewhat more efficient than the previously mentioned supports. The entire criteria for establishing the value of any type of support is control of edema; a support which does not prevent swelling, when the patient is active, is valueless; one which prevents swelling is adequate. We prefer a pure rubber roller bandage, 3 inches wide and 15 feet long. Of the three weights available, the proper one prescribed for any specific patient depends on the difficulty in controlling the edema. Ordinarily, the bandage is applied over a lisle stocking, beginning by making two turns about the foot, two figure-of-eight turns about the ankle, and progressing up the extremity to the knee. The toes and part of the heel are left exposed. The bandage should be removed and applied in the same manner each time, as it becomes shaped to the extremity on repeated use. If it is applied too tightly, the toes become discolored, cold, and numb. If it is applied too loosely, edema results. Patients soon become adept at bandaging their legs efficiently. The bandage should be removed at midday and reapplied over a dry stocking after the patient has rested for an hour. The same procedure is repeated at night if

the patient is active. If he remains home, he may remove the bandage and elevate the leg, while sitting. Patients object to wearing the bandages because of the inconvenience in applying them repeatedly, the slight discomfort, and their unsightly appearance. This is particularly true of women, who object to the appearance of the bandaged limb. Frequently, a well-fitting elastic stocking may be used for "dress" occasions and the use of the heavier rubber bandage may be reserved for ordinary activity. It is well to point out to women that the lymphedematous leg has an abnormal appearance which the bandage increases but little, and to emphasize that uncontrolled edema almost invariably causes a gradual increase in the size of the limb. We have no information regarding how long the bandage should be worn; in some instances, it must be used indefinitely; in others,

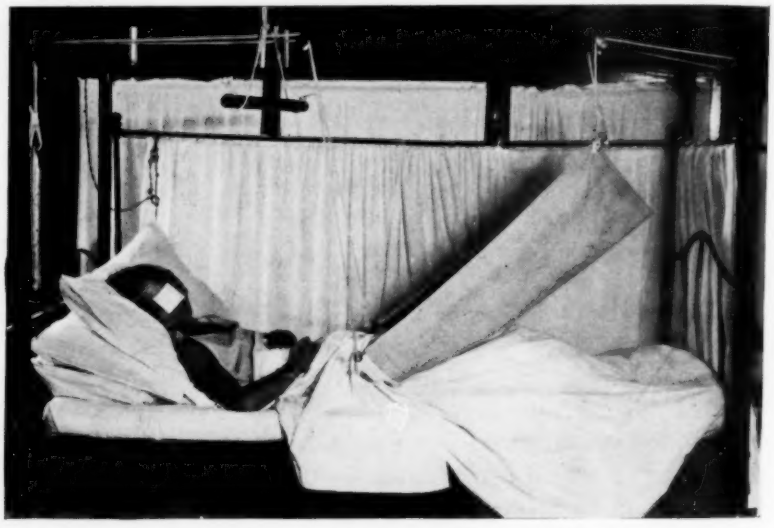

FIG. 7. Sling for elevating leg to reduce lymphedematous swelling.

improvement in circulation of the lymph may occur. Once every month or so, the bandage can be left off for a day as a trial. If edema reappears, the support must be worn again.

Treatment and Prevention of Inflammation. The attacks of acute lymphangitis ordinarily subside spontaneously but recovery appears to be hastened by elevation of the limb and by the application of hot moist packs. When reactions are severe, streptococcus antitoxins, such as those which are used in the treatment of erysipelas or scarlet fever, or polyvalent serums may be used. Blood serum from patients who recently have recovered from an attack of acute lymphangitis and cellulitis may be of value. We have never observed patients to whom we thought it necessary to give antitoxins or convalescent serum for an episode of acute inflammation.

Almost the entire problem, as far as infection is concerned, is the pre-

vention of attacks. Unfortunately, we have no proved way of accomplishing this. We have felt that some commercial preparations, such as streptobacterin, when administered for a long period have been helpful but we can offer no direct evidence. More logical would be the manufacture of an autogenous vaccine from organisms which have been isolated from the tissues at the beginning of the attacks. Again, we have no definite evidence that organisms can be isolated regularly during attacks or that a vaccine would be effective in preventing them. We hope that studies with animals which have lymphedema will demonstrate the value of this method. The periodic injection of a therapeutic amount of streptococcus antiserum every few weeks may be of value. Care should be taken to avoid serum reactions. Portals of entry, such as are present between the toes in the presence of trichophytosis, should be removed. When attacks of acute inflammation recur, trichophytosis should always be suspected and vigorously treated, if present.

Surgical Treatment

The necessity of surgical treatment of lymphedema is a frank admission of failure of medical treatment in those instances in which the best medical treatment has been carried out. In many instances, however, surgical treatment is necessary because medical treatment has been carried out inefficiently or not at all. Selection of cases of lymphedema for surgical treatment depends on the etiology and severity of the lesion. There is no need to perform the operation in cases in which malignancy exists or in cases in which causative conditions of greater importance than lymphedema, such as Hodgkin's disease or pelvic tumors, are present. Unfortunately, we cannot promise the patient who has mild lymphedema a great deal of benefit. The leg can be restored to normal size and to nearly normal shape, but there is no assurance that such restoration will be in any way permanent unless an adequate type of supporting bandage is worn for an indefinite period. Therefore, the more severe the case, the more one can offer in the way of relief with surgical treatment. The history of attacks of cellulitis is not a contraindication to surgical treatment, but on the other hand, one can reasonably assure patients who have had recurrent attacks of cellulitis that the frequency of these attacks will be reduced. One should, of course, not operate during an attack of cellulitis.

The immediate preoperative care of the patient should consist of rest in bed for a few days, with the affected limb elevated continuously to reduce the edema. A sling, which supports the limb at an angle of at least 45°, should be used. Diuretics, such as salyrgan, and firm bandaging may hasten the disappearance of edema. In three to six days, as a rule, the amount of lymph in the limb will be minimal which will make the surgical procedure much easier than it would have been before.

The various surgical methods which have been used for the treatment of lymphedema have been reviewed by Ghormley and Overton. The pro-

cedure used at the clinic is that which was described originally by Kondoleon and modified by Sistrunk.

The actual operation should be carried out under spinal anesthesia, using a tourniquet, applied as high as possible on the affected limb and usually without the customary towel beneath it. Two incisions are made along one side of the thigh or arm, extending as high as the lymphedema, so that a long strip of skin may be excised in an elliptical manner. The amount of tissue that can be removed will depend on the width of the strip of skin between the two incisions. As much as possible should be removed in order to reduce the size of the extremity greatly. When the incisions have been made through the skin, the margins of skin to be left are undermined for a

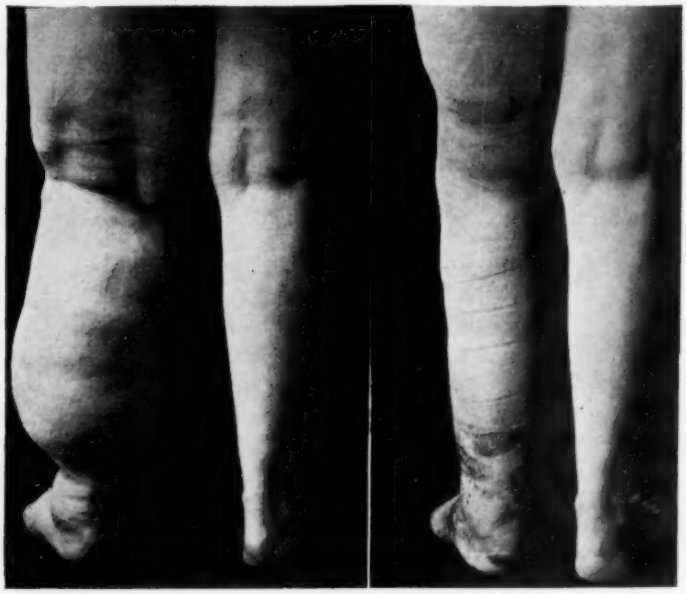

FIG. 8. Appearance of limb before operation and one year following operation for lymphedema.

distance on either side, approximating half of the circumference of the extremity. The skin, subcutaneous tissue, and as much as possible of fascia, except that at the intermuscular septa and at joint capsules, are removed in one piece. Care should be taken not to damage the main cutaneous nerves. After removal of the tissue, the wound should be closed with interrupted sutures. No attempt is made to secure hemostasis, only the larger branches of the veins being ligated. In closing the wound, one should not hesitate to apply as much tension as is necessary; considerable tension may be applied without fear of sloughing. Indeed, it is better to have some tension than to have an excess of skin remaining redundant. A pressure bandage is applied and the tourniquet released slowly, taking

several minutes to allow the circulation actually to return to normal. We believe this step to be of considerable importance as it is possible that the sudden flooding of the circulation with material from the large wound may have had something to do with the high incidence of surgical shock. The limbs are not elevated after the operation, so that materials from the wound get into the general circulation somewhat more slowly than if the limbs were elevated. Apparently, as a result of the methods mentioned, the incidence of postoperative shock in these cases has been reduced to almost zero.

After 10 days, the dressing is changed, and if healing has advanced sufficiently, the patient is allowed to be up. Adequate bandaging, such as that described with the medical treatment, is necessary for an indefinite period. Crutches or cane are unnecessary when the patient resumes walking.

It is customary to wait from three to six months between operations. That is to say, we treat one side of an extremity and allow healing to become complete before operating on the other side. Occasionally, patients get enough improvement from the operation on one side to justify omitting the second stage, but, as a rule, a much better result will be obtained if both sides are subjected to operative treatment.

Ghormley and Overton recently have reviewed the results in 64 cases of lymphedema, in which the condition was treated surgically in the past 10 years. In 41 of these cases, there was improvement of varying degrees; no improvement was noted in eight cases; in six cases the patients had died; and in nine cases, the patients had not been traced.

Recurrent infection such as cellulitis and lymphangitis, which had been present in 25 instances preoperatively, was worse after operation than it had been before, in six cases; was improved in nine cases; and had disappeared in 11 instances, as a result of the operation.

We are not wholly satisfied with the operation described. There is considerable doubt that the benefit, which follows, results from that effect which Kondoleon originally intended, namely, anastomosis of the superficial and the deep lymphatics, if, indeed, this actually occurs. Since the obstruction in many instances appears to be in the lymphatic vessels within the pelvis, little or no benefit would follow the shunting of lymph flow into the deep vessels in the leg, as these are continuous with the obstructed lymph vessels. The operation appears to us to be predominantly a plastic procedure, removing large valveless lymph spaces and hypertrophied connective tissue. As such, it is not a physiologic procedure but simply a plastic one, which corrects deformity. Since lymphedema has been produced experimentally, it is to be hoped that better methods of surgical treatment will be discovered. Perhaps the most satisfactory procedure will be found to be a combination of the plastic operation of Kondoleon, and one designed to carry the lymph around the area of obstruction, such as anastomosis of the lymphatic vessels of the extremity with those of the trunk. Such a procedure as the latter has been described by Gillies and Fraser.

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THE EXPERIMENTAL AND PATHOLOGICAL ASPECTS OF SILICOSIS *

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THE purpose of this paper is to present certain aspects of human and experimental silicosis and to report some of the recent advances in this subject, along with some of the difficulties that are being encountered by its investigators.

Silicosis is an industrial disease of increasing importance that has been recognized by the clinician for the past hundred years. Formerly this condition was known by many names, such as grinder's rot, miner's phthisis and stonemason's lung. Gradually these occupational diseases were found to be associated with the inhalation of dust in the corresponding trades. The pathological lesions in these pulmonary conditions were essentially the same and from statistical data some form of finely particulate silica was thought to be the harmful ingredient in the inhaled dust. Today this condition is recognized as a type of pneumonokoniosis and is known more or less universally as pulmonary silicosis.

The investigators of any pulmonary disease caused by the inhalation of silicon compounds are chiefly concerned with the extremely fine particles that gain entry to and are retained by the lung. In silicosis the majority of these particles are under three microns and very few are over five microns in their greatest diameter. The minuteness of these particles is appreciated if it is kept in mind that the diameter of a streptococcus is one micron.

The chemist can quantitatively analyze siliceous material for its constituent elements, such as silicon, potassium and aluminium. Analysts express the quantity of these elements in terms of the corresponding oxides. They therefore express the amount of silicon in terms of silica, though all the silicon may have existed in the form of a silicate, none actually being present as silica. This is misleading to the pathologist unless the significance of such an expression is borne in mind.

The mineralogist by the microscopic observation of the optical properties of small fragments of siliceous crystals can specifically identify fragments as small as ten microns. According to Knopff, particles under ten microns cannot be specifically identified by this method.

The physicist by the aid of the spectroscope or roentgen-ray absorption spectra could specifically identify the most finely particulate material if he were dealing with a single compound, but when a variety of compounds are present these methods have also failed.

This inability specifically to identify finely particulate siliceous material is a stumbling block to the investigators working on the problem of silicosis.

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From the Department of Medical Research, University of Toronto.

It is a phase of the problem now receiving considerable attention, and from present indications may be solved in the near future.

The pathologist also has his difficulties. He relies on the chemist for a quantitative estimation of the silicon present in a tissue, but he must be able to demonstrate the siliceous material microscopically in order to study any tissue reaction that may be associated with its presence.

The most satisfactory method for the histological demonstration of siliceous material in tissue is that of microincineration. This consists of placing an ordinary histological section on a glass slide and heating it to a dull red until all the organic substances are removed. The inorganic material is left behind and is so remarkably in situ that the skeletons of single cells can be identified. This ash can be treated with aqua regia to remove the soluble chlorides without disturbing its pattern. The acid insoluble ash consists almost entirely of siliceous material. Serial sections permit the orientation of the total inorganic and the siliceous ash to the histological structures in which they were contained. This method also has the advantage of unmasking the siliceous material that is obscured in the ordinary section by carbonaceous pigment or rendered occult by hydration.

A knowledge of the amount, identity and distribution of the siliceous material that may exist in the tissues of a healthy individual is essential before silicotic lesions can be appreciated.

Recent investigations by McNally in this country, and Fowether in England, place the amount of siliceous material in the lungs of normal individuals as 100 to 200 milligrams per cent dry weight. Belt, King and I have recently investigated the amount of siliceous material in the tissues of individuals who had been exposed only to the dust present in the ordinary atmosphere and whose tissues showed no evidence of any fibrosis associated with the siliceous material present. Thirty-five tissue specimens were studied from each of six individuals coming to autopsy, the ages being from two months to 78 years. Most of these tissues were healthy but some were selected that presented pathological lesions, such as inflammation and new growth. These tissues were divided into two parts. The first was assayed chemically for the amount of silicon, which was expressed as equivalent silica. The second was cut in paraffin so that histological sections could be studied and the technic of microincineration used. This allowed a study of the amount and distribution of the siliceous material. The specific identity of the silicon compounds could not be ascertained. The amount of siliceous material in the tissues apart from the lungs was approximately 25 milligrams per cent dry weight of tissue. This amount was practically the same at all ages, and in all tissue whether healthy or diseased. Microincineration showed the siliceous material to be distributed diffusely throughout.

Particular attention was paid to the lungs and pulmonary lymphatics, as they contained large amounts of siliceous material. On this account 30 additional normal lungs were studied to enlarge the series. In the total 36

lungs we found that the amount of siliceous material was the same at birth as in the other tissues, but that there was a gradual increase until the third or fourth decade, when a level of 100 to 200 milligrams per cent was reached that more or less persisted in the later decades. This suggests that about the third or fourth decade a balance is reached between the siliceous material retained by the lung and that removed from the lungs by the pulmonary lymphatics.

The amount of siliceous material in the peribronchial and mediastinal lymphatic glands increases proportionately with the age of the individual. From the beginning of the third decade these glands contain tremendous amounts of siliceous material when compared with the other tissues, usually 2000 to 4000 milligrams per cent and not uncommonly in advanced years, 5000 milligrams per cent dry weight. These glands contain from 10 to 25 times as much siliceous material as the corresponding lung tissue and from 50 to 80 times as much as the other tissues, apart from the lungs. In these lungs and pulmonary lymphatic tissues the siliceous material was not evident in the stained sections, as it was constantly associated with and obscured by the ever-present black carbonaceous pigment. This siliceous material was demonstrated by the technic of microincineration and was found to be distributed throughout the lung and lymphatic tissue in collections of varying size. The concentration of the siliceous material in these collections was quite uniform.

These findings make several points clear. First large amounts of siliceous material can exist in the pulmonary lymphatics for long periods without producing any pathological lesions. Secondly, the black pigment in lung or pulmonary lymphatic tissue is almost without exception a guide to the amount and distribution of the siliceous material present. Thirdly, the inclusion of peribronchial lymphatic nodes in the tissue of a lung suspected of being silicotic will give a false impression of the amount of siliceous material present.

Investigators of the pneumonokonioses have been much more interested in the dust that is retained by the lung and the results produced by its presence, than in the dust temporarily held by the lung and eliminated normally in the bronchial mucus. The bronchial tree from the larynx to the respiratory bronchioles is lined by tubular escalators formed by the layer of mucus continuously propelled toward the larynx by ciliary movement. Dust particles coming in contact with this sheet of mucus are soon eliminated in the sputum.

The functional unit of the lung consists of the respiratory bronchiole and the atria and alveoli that arise from it. This structure is conveniently compared to a bunch of grapes, the main stem the respiratory bronchiole, the stem branches the atria and the grapes the alveoli.

Dust coming in contact with the alveolar walls could be eliminated by the healthy lung in several ways. It would appear that the respiratory

movement of the alveoli might physically extrude some of the dust particles. The alveolar phagocytes having engulfed dust particles might carry them to the bronchiolar mucus. The mucus of the bronchial tree is supplied by glands and goblet cells that become fewer as the periphery of the tree is approached. It is assumed that the alveoli are lined by a layer of fluid that is continuous with the fluid lining the terminal bronchioles. If such be the case, the terminal bronchioles must derive much of their fluid by pulling it from the alveoli by ciliary movement. If this hypothesis is correct, this fluid layer should be capable of removing much dust.

The failure of this mechanism of elimination allows dust that comes in contact with the alveolar walls to collect and remain in the lung. This incarcerated dust is engulfed by the alveolar monocytes, which, not being able to leave by the normal exit, collect in the respiratory bronchioles and pass through the walls of these structures to the lymphatic channels. When such a condition exists the ultimate result depends upon the amount and nature of the dust that gains access to the pulmonary lymphatics or remains in the smaller air passages.

The first and most important lesion in any pneumonokoniosis is the functional failure of this mechanism of elimination. Strachan and Simson of South Africa, state that in silicosis a dry bronchiolitis is a constant feature and may be an important determining factor in the lung invasion. The pathogenesis of the failure of this mechanism is not known. It may be damaged in several ways. Chronic bronchitis of infective origin may produce marked damage. The chemical presence of certain dust particles may also produce marked damage. The particles of dust that reach the lung alveoli are so fine that their rate of solution is comparatively rapid.

Silica in the form of finely particulate quartz, when placed in the tissues, soon takes up water to form a substance that is toxic. The first action of such a substance in the bronchiolar mucus would probably cause slowing of ciliary movement. This in turn would tend to prevent proper elimination and allow a sufficient concentration of the toxic substance to produce anatomical change. In some industries irritating gases may accompany the inhaled dust. Gases such as the oxides of carbon, sulphur and nitrogen when in solution give rise to the corresponding acids.

Recently Robson, King and I subjected rabbits to an atmosphere containing a concentration of nitrogen dioxide 1 in 10,000, and of sulphur dioxide 1 in 20,000. The rabbits were exposed to this gas mixture for two hours daily five days a week. In the course of a few weeks all these animals showed diffuse lesions in the bronchial tree characterized by loss of cilia, degeneration and desquamation of the epithelium and in some cases a metaplastic change from columnar-ciliated to non-ciliated stratified epithelium. There was also a lymphocytic infiltration of the walls of the bronchial tree. These lungs did not show any nodular fibrosis. When finely particulate quartz was added to the atmosphere along with these gases, all the animals exposed for periods of 10 weeks or more showed nodular fibrosis con-

taining large amounts of siliceous material. This fibrosis was first seen in the alveoli and later in the peribronchial lymphatic aggregations and mediastinal lymphatic glands. Animals exposed to quartz dust alone required an exposure five times as long before similar lesions are produced.

Our interpretation of these experiments was that the addition of the gas to the atmosphere quickly damaged the normal mechanism of dust excretion, and allowed the incarceration of relatively large amounts of quartz dust in the lungs in a comparatively short period.

In industries where silicosis is common, certain men remain healthy for many years though exposed to the same atmosphere in which other men develop silicosis in much shorter periods. It is probable that this individual susceptibility depends upon the functional activity of the mechanism of normal dust excretion by way of the bronchial mucus.

It is frequently of importance to ascertain experimentally if a given dust is capable of producing silicosis. There are several ways in which this may be investigated. Dust can be added to tissue cultures and its effect on the behavior of the cells observed microscopically. Animals can be exposed to a dusty atmosphere and the lungs examined at intervals. This method most closely simulates human exposure and valuable information has been obtained by Gardner at Saranac Lake by this method. Large numbers of animals are required as the exposure is necessarily long and fatal concurrent infections are numerous. Kettle injects a suspension of dust in saline into a lung by means of a catheter. This allows a large amount of dust to gain entry and remain in a lung where its effects may be followed. The time interval is greatly lessened but infection may be introduced. Sayers has studied the reaction produced by injecting dust into the peritoneal cavity. The subcutaneous injection of dust provides a convenient way of following its reaction. Dust injected intravenously is engulfed principally by the reticulo-endothelial cells of the liver, spleen and bone marrow, where its action may be followed. It must be kept in mind that the reaction produced by a dust in the lungs may not be identical with the reaction produced in other tissues.

Our knowledge is meagre concerning the tissue reaction produced by pure siliceous compounds that have been specifically identified and consist of particles of known size. Silicosis-producing industrial dusts are almost always mixtures of various substances both organic and inorganic. Ways of fractionating these dusts into their component parts must be found so that these components can be studied individually. Most authorities agree that finely particulate sterile silica in any of its forms when present in most tissues produces a nodular fibrosis that closely resembles the lesions in a human silicotic lung.

The size of the particles is very important. Gardner has shown that the injection of quartz particles one to three microns in diameter will produce a nodular silicotic fibrosis in the same period of time that particles six to twelve microns in diameter produce only a foreign body reaction. Banting has

not been able to produce silicotic nodules by the subcutaneous injection of quartz particles of colloidal size. It would seem that the larger particles dissolve so slowly that the dissolved silica is diluted and carried away by the lymph and blood sufficiently fast to prevent the formation of toxic concentrations. The particles of colloidal size dissolve very rapidly but represent such a minute amount of dissolved silica that it also can be removed before damage is done. In pulmonary silicosis the particles that produce fibrosis are those that are small enough to be engulfed by the monocytes and to dissolve quickly, yet large enough to give rise to an amount of dissolved silica that cannot be diluted or removed fast enough to prevent the formation of a toxic concentration.

The subcutaneous injection of finely particulate quartz results in a primary acute inflammation. The acute reaction subsides about the fifth day when the monocytes appear. These phagocytes engulf the quartz particles. The engulfed quartz particles are at first doubly refractive, but after a few weeks they lose this property, indicating their hydration. These monocytes degenerate, the degeneration coinciding with the hydration of the quartz. Other monocytes engulf this débris and in this way the amount of hydrated quartz contained in each monocyte is lessened. Eventually the monocytes contain an amount of hydrated quartz compatible with the life of these cells for longer periods. The monocytes then become arranged in groups, elongate, lose their power of motility, and take on the appearance of fibrous connective tissue cells. We have followed this reaction in many tissues and have found the reaction to be essentially the same in all tissues. Some difference of opinion exists as to the origin of the fibrous tissue in a silicotic nodule, but the recent work of Moen substantiates their monocytic origin. He was able to grow in tissue culture colonies of fibrous connective tissue cells from single monocytes.

The process of fibrosis in a silicotic lung is essentially the same. The distribution of the fibrotic areas depends on the amount of finely particulate silica retained by the lungs in a given period. If the silica dust is retained in small amounts over a comparatively long period it is removed from the periphery of the lung by the monocytes to the lymphatic glands of the mediastinum where fibrosis is first seen. As these glands are blocked by the fibrosis, subsequent fibrosis is peripheralward in the peribronchial lymphatic glands and aggregations until fibrosis takes place in the periphery of the lung itself. As this fibrosis is progressing the lymphatic drainage to the pleura transports dust to that part of the lung, resulting in fibrosis. This type constitutes the commonest form of the disease, that of chronic silicosis, requiring from five to 25 years for its development. If large amounts of silica are retained by the lungs in a short period of time the order of fibrosis seen in chronic silicosis is reversed. These cases constitute acute silicosis as seen in the lungs of abrasive soap workers reported by Chapman of Boston.

Much attention has been paid recently to the possibility that the retention of inhaled silicates might give rise to a fibrosis resembling that of silicosis. Asbestosis is a definite pneumonokoniosis due to the reaction produced by the retention of asbestos fibers in the lung. Asbestos is a hydrous magnesium silicate. In the lung the asbestos fibers become hydrated and undergo partial disintegration. This change is associated with the production of fibrosis and suggests that the associated fibrosis is due to the chemical presence and not the physical presence of this silicate. It is not known whether the fibrosis is due to the dissolved asbestos or whether the magnesium is leached out leaving silicic acid which produces the damage. If such is the case, and convincing evidence has been brought forward recently by Berger, asbestosis is an indirect form of silicosis.

Sericite, a potassium aluminium silicate in the physical form of a fibrous secondary mica, has received much attention during the past two years. Its presence in silicotic nodules has been recognized by the South African workers for many years. Jones, a mineralogist, has attached great importance to its presence in silicotic lungs. Although he does not definitely so state, he strongly infers that the fibrosis of silicosis is due to the physical presence of the sericite fibers. From our experimental work we cannot say that sericite is entirely innocuous. We do know, however, that sericite can remain in lung, lymphatic, or subcutaneous tissues for periods of a year without producing anything but a foreign body reaction and shows no evidence of physical change by the tissue fluids. Fibers of sericite can be demonstrated in the pulmonary lymphatic glands of healthy individuals and are not associated with any fibrosis.

Tuberculosis is usually the immediate cause of death in silicosis. Many reasons have been put forward to explain the susceptibility of silicotics to this type of infection. The activation of quiescent lesions, an increased virulence of the organism, a more suitable medium for its growth, a blockage of the lymphatics, a lowered resistance both local and general, increased exposure to infection, have all been advanced. This is a subject in itself and can be mentioned only parenthetically here.

I have tried to present some of the conceptions of silicosis that are held by the members of the Department of Medical Research in the University of Toronto. We feel that this problem is by no means solved, and its solution will be brought about only by the coöperation of the medical profession with the chemist, the mineralogist, the physicist and the industrial engineer.

ACCESSORY SINUS INFECTION; ITS RELATION TO MASTOID AND LUNG INFECTIONS *

By Willis F. Manges, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

Nasal accessory sinus disease is one of the most important clinical subjects that we have to consider today. It is more frequently overlooked and more inadequately treated than almost any other disease of real consequence. If one reflects that every "cold in the head" is a possible attack of sinusitis, that each attack is apt to leave some little trace of its presence, increased by subsequent attacks and encouraging still other attacks, so that finally there is a chronic, permanent sinus infection, easily tolerated, a latent source of infection for all other portions of the body, then it becomes evident just how common and prevalent is sinusitis, why so little attention is paid to it in its earlier stages, and how potentially troublesome it may be.

The common cold may not be infectious in the first day or more, but in almost every case the secretions become mucopurulent within a few days. The mucous membrane of the sinuses is involved in the inflammation, as are the nasopharyngeal membranes. The virulence of the infective bacteria and the interference with drainage determine the severity of the individual attack.

The common "head cold" *initiates* the events considered here. A child does not first get bronchitis and then the head cold, nor does earache precede the head cold. Invariably, one may say, the nasopharyngeal lesion comes first.

It is important, too, to realize that the head cold quite frequently begins in infancy and recurs repeatedly through those first few years when the child is unable to make known his troubles except by coughing or crying. Probably very few children escape the experience. Fortunately, many of them escape the evil complications of ear infection or lung infection, but it is certain that the leading event or the principal element in the etiology of the majority of cases of infected ears or mastoids, of many of the acute, and of a still larger percentage of the chronic lung infections, is that first attack of common cold in the head, whether it begins in infancy or in later years.

It is well to consider both ear and lung lesions in the same paper as complications of sinus infection, because both of these structures are subject to direct invasion by infected material from the sinuses, and both complications are present frequently in the same patient. Either or both may occur with the first attack of sinusitis, or with any subsequent attack. More frequently the pulmonary complications develop gradually with repeated

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935.

attacks of sinusitis. This is particularly true of the chronic lesions, such as bronchitis, bronchiectasis, and asthma.

The most common route of invasion from the sinuses to the ears is by way of the eustachian tube, and to the lungs by way of the pharynx, larynx, trachea, and bronchi. It is essentially a foreign body invasion, blown into the ear and drawn into the bronchi. This applies especially to bilateral bronchiectasis, and seems to be the best explanation of the fact that bronchiectasis is almost always maximal in the most dependent portions of the lungs, just where the majority of all kinds of foreign bodies tend to go. With sinusitis the individual, foreign, infection-bearing bodies may be very small but so numerous that sooner or later both lungs are involved.

This, of course, is not the only route. The lymph channels furnish another, as Mullin [13] found after careful research. I also believe, as the late J. C. Wilson [18] taught, that the inflammation in the nasopharynx travels by continuity into the larynx, trachea, and bronchi. It is entirely probable, too, that such extension occurs to the middle ear. Certainly, the lung lesions vary sufficiently to suggest various routes of invasion. In one, the involvement is mainly in the lymphatic structures at the roots of the lungs; in others, there is almost uniform peribronchial thickening evenly distributed throughout the lungs; others have bronchiectasis in the lower lobes; still others have more or less extensive adhesions or pleural thickening at the base; and some have definite allergic manifestations as the result of the sinus infection, and without lung changes other than emphysema from repeated attacks of asthma. Many patients with chronic lung infection occasionally have dyspnea of varying degree, because their exudate is at times more tenacious and interferes more with respiration, and particularly, with expiration. Under such conditions an erroneous diagnosis of asthma is frequently made.

The route of bacterial invasion is of relatively little importance. What matters materially is that we should all admit and recognize the sequence of events. Both experimental and clinical observations on the part of those definitely interested in the subject attest this sequence.

Cullom,[5] in speaking of the various complications of sinus disease, said: "I wish to emphasize one that has been brought home to me forcibly. I was somewhat surprised in reviewing our cases of acute mastoid abscess to find that practically all of our cases done during the last four years had empyema of one or more sinuses. There should be nothing surprising in the fact, however, when we consider that the pus draining into the post nasal space passes over the orifice of the eustachian tube. The surprising thing is that they do not all get infection of the ears."

In a more recent paper, Cullom [6] reports that 85 per cent of more than 100 patients with mastoiditis had positive evidence of sinus disease and that in all of them there was a diseased sinus on the same side as the infected mastoid.

Fowler [7] considers that the swimming pool and the nasal douche varieties of mastoiditis are analogous to those from sinus infection. Eighty-six per cent of Fowler's mastoid patients had positive roentgen-ray evidence of sinus disease.

Campbell [2] found that practically all of 150 consecutive patients with ear infection had sinus infection, which he looked upon as an etiologic factor in the production of otitis. He believes that no child has reached the age of one year without having a sinus infection.

In a later paper, Campbell [3] reports the study of 130 patients with lobar or bronchopneumonia. The ages varied from three months to 90 years—only seven were adults. Evidence of sinus disease was found in all. He also noted that of this group there was also ear involvement in 80 per cent.

Keller [9] says: "The head cold is the leading causative factor in the production of acute catarrhal otitis media," and also in acute purulent otitis media.

Musser [14] gives a clear picture of the sequence and relation of sinus infection and the two complications considered here when he describes "Infectious Cold." He says that the disease terminates sometimes within a few days without further symptoms, and at this time the true virus infection ends. "In most instances, however, the discharge gradually becomes more purulent and less abundant. This marks the pyogenic stage of the disease and it is in this period that sinusitis and otitis may occur. Even more serious troubles may develop, including pneumonia, either lobar or lobular." In this excellent textbook he also emphasizes the sinuses as a source of infection in chronic bronchitis and bronchiectasis.

Wasson and Waltz [17] made a study of 100 children from three months to eleven years of age. Of the 93 over six months of age, 71 show the presence of sinus disease. Of the 93, 36 were two and a half years of age or less, and lung lesions were not estimated. Of the remaining 57, there was no evidence of lung disease in 22, but in 28 there was roentgen-ray evidence of non-tuberculous infection. Two had non-active tuberculosis with superimposed upper respiratory tract disease, and five had non-active tuberculosis with calcification or fibrosis. All of these children had roentgen-ray examinations of the sinuses and chest every three months, so that the diagnosis was based on a large number of examinations of each case. Seventy-one of the 93 from six months to eleven years had evidence of sinus disease. Twenty-eight of the 57 had non-tuberculous infection of the lungs. This entire group was supposed to be made up of children healthy from birth.

Quinn and Meyer [16] have observed from the study of 38 cases of bronchiectasis, that as a class the patients with sinusitis were considerably younger than those without. They also found that 77.2 per cent of the patients with sinus disease had bilateral bronchiectasis. The majority of their group had no symptoms of sinusitis.

These authors conducted an interesting series of experiments, dropping

iodized oil through catheters into the posterior nares of 11 sleeping patients, and they found that in five the iodized oil went into the lungs. The significance of this result must be apparent. I dare say that all of these patients were asleep in the recumbent posture. In the prone or lateral postures, I believe the iodized oil would not have gone into the bronchi.

Pierson [15] has reported two cases of pneumonia associated with fibrosis from oil deposits in the lungs in quite young children, one of whom had had oil dropped into the nose to control mucus and cough; the other had been given mineral oil by mouth for constipation. He also gives references of other such cases.

In a study of 200 patients with bilateral bronchiectasis, Clerf [4] found that 82.4 per cent had sinus disease. I had the opportunity of studying many of Clerf's cases and I know that quite a few of them were in children. He also notes the relative infrequency of sinus disease in association with unilateral bronchiectasis, which fact refutes the argument that sinus disease results from bronchiectasis. He says that bronchiectasis is not cured by treatment of the sinus disease, but treatment of sinus disease in early chronic cough is preventive of bronchiectasis.

In an analysis of the roentgen-ray findings in 354 asthmatic patients, I [11] found positive evidence of sinus disease in 60 per cent. Doubtful roentgenographic evidence was not accepted and in none of the patients was the diagnosis checked by means of the injection of iodized oil. This percentage, I am sure, is too low for any such group. The most important finding in this study was the fact that 85 per cent of the patients showing evidence of sinus disease also had roentgen-ray evidence of lung changes. In a former paper, I [12] reviewed the literature up to 1930 and found 20 excellent articles, all of them expressing the idea that sinus disease is responsible for the lung changes that follow.

During the past several years it has been my custom to make at least one or two roentgenograms of the accessory sinuses of patients of all ages sent to me for study of the lungs in whom I could find no evidence of tuberculosis, but who showed evidence of other infectious processes. Sinus disease has been found in a surprisingly large number. The striking fact in most instances is that neither the patient nor the physician has had any thought of sinus disease being present. Two typical examples of this combination may emphasize this point. Recently a medical student was sent to me for roentgenographic examination of his chest because of a severe persistent cough. As there was fairly extensive peribronchial thickening rather evenly distributed throughout his lungs, I had him return for sinus study and for questioning. So far as he knew, he had never had sinus disease, but had had repeated attacks of prolonged severe cough for a number of years. One previous rhinological examination had revealed nothing. A roentgenogram of the sinuses shows a completely opaque antrum on one side. At the time, he had no subjective signs of the disease and no nasal discharge. A sub-

sequent examination shows that the maxillary antrum has drained but that there is still definite evidence of thickening of the lining membrane.

Another patient, the daughter of a physician, was referred for study of the lungs and heart. Cough was excessive, and one physician thought she had a heart lesion. Her root structures were enlarged to some extent and this led me to make a study of the sinuses, which revealed a completely opaque antrum. I was surprised about a week later when I was told that a rhinologist had punctured the antrum but found no evidence of pus. A subsequent roentgenographic study showed a markedly thickened lining membrane with a small amount of air in the antrum. Obviously, it would be a mistake not to try to improve this condition.

I have also made roentgenograms to include the sinuses in all cases of mastoiditis, and again in the majority, especially of acute mastoid cases, there is evidence of sinus disease, but the subjective symptoms are all referable to the ear.

It seems quite unfortunate that sinus disease, except in the fulminating type, does not produce more active subjective symptoms. This must be the reason it is so generally overlooked, not only by the general practitioner, but also by the pediatrician, the medical consultant, the otologist, and even the rhinologist.

Certainly much depends on the early diagnosis, and since the local subjective symptoms are, as a rule, so slight, one should consider what remote signs should be thought to indicate probable sinus disease. I look upon the following as strongly suggestive signs of sinus disease: Cold in the head; running nose, especially if discharge is mucopurulent in character; postnasal drip; *cough,* especially persistent, prolonged cough, with or without expectoration, with or without fever; any slight change in the character of the voice, such as nasal twang; hoarseness or loss of voice; repeated attacks of pneumonia; asthma, particularly in children, but also at any other age; other forms of dyspnea; earache or discharging ear; mastoid disease; headache, neuralgia, etc.; and, in fact, any other condition that might be considered due to focal infection.

Complete diagnosis depends upon what the rhinologist can see by direct inspection, by transillumination of the sinuses, or by puncture or other effort to obtain the contents of the sinuses. Of even more importance is the roentgenographic study of the sinuses, if it is done properly and accurately. This also offers the best means of determining results of treatment, and the only means of obtaining a visible permanent record. Injection of iodized oil is sometimes necessary to make a positive or negative diagnosis when there is any doubt. By this means alone, very slight thickening of the lining membrane can be demonstrated. Kistner [10] considers thickening of as little as one-half millimeter strongly suspicious of disease. He believes the chronic, nonsuppurative, thickened membrane type of sinusitis may be the more dangerous because it usually harbors streptococci, whereas the active suppurative type is most frequently staphylococcic. Other forms of bacteria

are also found, and in all types of sinus disease he found through cultures taken at operation the following in their order of frequency and predominance: streptococcus, staphylococcus, *Bacillus Friedlander, Micrococcus catarrhalis,* and *Bacillus influenzae.*

Campbell finds the use of the nasoscope the most satisfactory means of making a diagnosis of sinus disease in infants. On the other hand I have confidence in the roentgenographic method, but it does sometimes require a great deal of patience, and no small amount of ingenuity, to obtain satisfactory films of frightened children. With coöperation on the part of the patient, however, the roentgenographic study is by all means the most important part of the diagnostic procedure.

Treatment, obviously, cannot be adequate in the early stages when satisfactory results should be available, unless the pediatrician, the general practitioner, the medical consultant, and all the involved specialists will regard seriously the head cold and make certain that one or more of the sinuses do not contain purulent exudate, thickened membrane, or polyps, after the cold is apparently gone. Prevention of subsequent attacks and of the chronic active stage should be the object of any plan of treatment.

Cullom says that the treatment of acute sinusitis is medical and of the chronic type is surgical. Hurd [8] in speaking of the surgical treatment of chronic sinusitis in the patient having asthma says it must be radical if undertaken at all.

Butler and Woolley [1] in reporting the results of roentgen therapy in 450 patients with chronic sinusitis say that 36 per cent are entirely relieved, 55 per cent definitely improved, and 9 per cent show little or no improvement. I have not as yet tabulated my own cases, but can testify to the value of such treatment of the sinuses, particularly in a selected group of asthmatics. The results may not be permanent because the sinusitis may recur. The soil is not permanently changed. I am not competent to discuss the various other methods of treatment, but I am certain that there is much to be desired; and I am also certain that there are relatively few physicians who take the matter as seriously as they should at the time when something might be accomplished. It is remarkable how much improvement may follow in the lung lesions, as well as the sinus disease, with skillful attention and treatment.

I have recently had return for reëxamination a group of patients, mostly children, in whom I previously found unsuspected sinus disease, when they were sent for roentgenographic study of the lungs. The invariable result has been that, when the sinuses have shown improvement, the lungs also have been more clear, and there has been definite improvement in general health. On the other hand, in those patients who show no improvement in the sinus condition, the lung lesions have progressed. Once it is established, bronchiectasis is not easily eliminated, but even so, the general health of the patient will improve if the sinus infection is improved.

Nature does sometimes cure a mastoid lesion by producing a contraction

and sclerosis in the cell structure, but for the most part, radical surgery is essential to cure.

Summary

Nasal accessory sinus disease is responsible for a large number of serious complications particularly in the ears and lungs, but also in other parts of the body.

The common head cold or infectious cold is the first stage of the sinusitis. This period is the one in which most can be gained by proper treatment.

The various types of lung lesions suggest more than one route of invasion of the infection from the sinuses to the lungs. The infection in the middle ear is probably carried there through the eustachian tube, either by being blown in or by continuity of tissue.

Subjective symptoms are frequently absent when the sinus disease is well established, whereas the subjective symptoms of the mastoid and lung complications are usually striking and sometimes quite distressing. The subjective symptoms of the complications should be considered symptoms of sinus disease. Acute mastoiditis very frequently is associated with a diseased sinus on the same side.

Sinus disease is present in a large percentage of asthmatics.

Bronchiectasis, associated with sinus infection, is bilateral in the majority of instances. Also, a large percentage of bilateral bronchiectasis has sinus disease. Bilateral bronchiectasis is to be considered incurable. It is frequently found in childhood.

Diagnosis of sinus disease should be based on direct inspection, on roentgen-ray examination, and on symptoms of the various complications.

The early ear and lung lesions respond to proper treatment of the accompanying sinusitis.

Attention to sinus disease in its early stages is extremely important.

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BASIC POINTS IN ROENTGEN-RAY STUDIES OF LUNG ANATOMY AND PATHOLOGY *

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BECAUSE of their permeability, the structure of the lungs is revealed by the roentgen-ray more clearly than is that of any other organ. On the basis of anatomical knowledge so acquired, pathological alterations may be recognized on stereoscopic films, and understood in direct proportion to that knowledge. The diagnosis of any disease is not complete unless it includes accurate localization, extent and character of the lesions. For example, the diagnosis of pulmonary tuberculosis is incomplete and almost useless when based solely on the report of tubercle bacilli in the sputum. Most important in the medical or surgical treatment of any pulmonary disease is accurate localization of the lesions, of which the first step is recognition of the lobe or lobes involved, and second, accurate orientation of the lesions within the lobes. Such localization must be based on an accurate knowledge of the bronchi and all of their divisions as they are seen on stereoscopic films. To be considered satisfactory for study, stereoscopic films must clearly show the trachea and its bifurcation into the right and left bronchus, the arch of the aorta passing over the left bronchus, the pulmonary arteries and the bronchial linear markings from apex to base of both lungs.

Descriptions of the roentgenological anatomy of the bronchi have been, in general, few and unsatisfactory. We therefore offer the following as a basis for a working classification. On the right side the bronchus to the upper lobe, given off above the pulmonary artery, is termed anatomically the eparterial bronchus. Within the upper lobe this bronchus breaks up into three main trunks. The vertebral trunk is the smallest, and extends directly upward from the top of the hilum shadow into the apex, running parallel to the vertebral column. The linear markings of this trunk all lie within the circle of the first rib. Thus a lesion limited to the apex of an upper lobe involves this area. The anterior and posterior branches of this division are so close together that it is often impossible to separate them unless a lesion is present in one or the other. Frequently a lesion in this area comes to the pleural surface along the mediastinum. The first interspace trunk, extending out from the hilum, passes outward and upward breaking up into linear markings under the pleura behind the first interspace. Thus a lesion limited to the anterior branch of the first interspace trunk will come to the surface below the clavicle. A lesion of the posterior branches of this trunk will come to the pleura just beneath the spine of the scapula. This is a very common location for an unrecognized tuberculous lesion or for the

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lodgement of a light weight foreign body. Usually lung abscess following surgical procedures in the mouth or throat is found in the right lower lobe but often it is overlooked in the posterior first interspace trunk area of the right upper lobe. The second interspace trunks are much larger and cover the greatest area in the lobe. The dependent branches spread out over the entire base of the upper lobe. The anterior branches end in linear markings behind the second and third interspaces; the posterior branches extend into the axilla and reach the pleura of the interlobar fissure between the upper and lower lobes.

The bronchus to the right middle lobe is given off below the pulmonary artery. It is visualized extending directly anteriorly from the hilum beneath the fourth and fifth interspaces. After the middle lobe bronchus is given off, the right main stem bronchus continues down into the lower lobe and divides into numerous branches which extend either to the posterior base of the lobe or anteriorly toward the interlobar pleural surface. To the apex of the lower lobe is given off a branch which has extremely important significance. This apical branch is given off from the main bronchus directly opposite the branch to the middle lobe. It courses directly backward pointing to the pleural surface under the seventh interspace posteriorly. This bronchus can only be seen on stereoscopic films because it directly overlies the hilum shadow. A lesion localized in this trunk area is present in the apex of the lower lobe. Localization here is extremely important. Too often we have seen abnormal densities in this area interpreted as being part of the hilum shadow when actually the density was produced by a pathological lesion in the apex of the lower lobe. This area is frequently the site of a lung abscess. Likewise in pulmonary tuberculosis it is common observation that when spread from an upper lobe lesion occurs it is likely to extend into the apex of the lower lobe. The frequent occurrence of a cavity in the upper lobe together with caseous bronchopneumonia in the apex of the lower lobe is well known. Recognition of involvement of the apex of the lower lobe can and should be made early.

On the roentgen-ray film the left bronchus is seen curving under the arch of the aorta. The bronchus to the left upper lobe is given off below the pulmonary artery and hence is anatomically given reference as an hyparterial bronchus. In the upper lobe the bronchus shows the same division of vertebral, first interspace and second interspace trunks with similar distributions as in the right upper lobe. But in addition there is a long branch which curves around the left border of the heart down into the lingual tip. This trunk is unusually prominent in heart conditions, especially mitral stenosis. The bronchus to the left lower lobe follows out exactly the same divisions and distributions as in the right lung.

This division and distribution of the bronchi is demonstrated by proper anatomic dissection of lungs. It is our routine procedure in performing postmortem dissection of the lungs for pathological study to follow out ana-

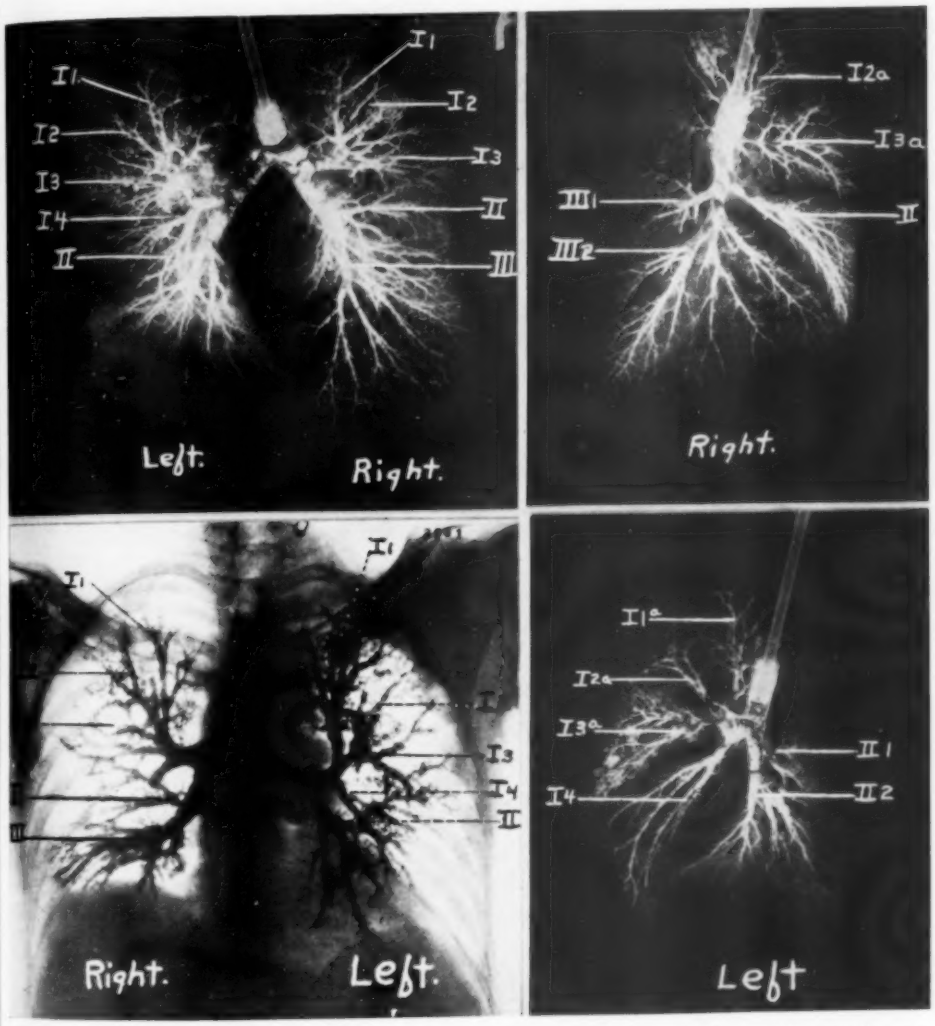

FIG. 1. Roentgen-rays of injected bronchi in lungs removed from body and in a cadaver.

Trunk Markings of Roentgen-Rays of Lungs

Right Lung

I. Upper Lobe Bronchus
  1. Vertebral Trunk
    (*a*) anterior division
    (*b*) posterior division
  2. First Interspace Trunk
    (*a*) anterior division
    (*b*) posterior division
  3. Second Interspace Trunk
    (*a*) anterior division
    (*b*) posterior division
II. Middle Lobe Bronchus
III. Lower Lobe Bronchus
  1. Apical Trunk
  2. Basal Trunks

Left Lung

I. Upper Lobe Bronchus
  1. Vertebral Trunk
    (*a*) anterior division
    (*b*) posterior division
  2. First Interspace Trunk
    (*a*) anterior division
    (*b*) posterior division
  3. Second Interspace Trunk
    (*a*) anterior division
    (*b*) posterior division
  4. Lingual Tip Trunk
II. Lower Lobe Bronchus
  1. Apical Trunk
  2. Basal Trunks

tomic dissection along the bronchi. First the main bronchus is opened and exposed in a longitudinal manner so as to show the structures at the hilum and the openings of the bronchi to each lobe. Then the bronchi are dissected by carefully slipping a small groove director into each division and with a long thin sharp knife cutting in the groove director and laying open the bronchus. In the upper lobes it is easier to open the bronchi in the lower portion of the lobe and then proceed upward. Demonstrations of these divisions of the bronchi are also made by the use of stereoscopic films of the lungs, removed from the body, in which the bronchi have been injected with an opaque substance. The specimens are prepared by injecting a thin paste of corn starch and bismuth in the trachea and bronchi of both lungs. Further demonstration of the bronchi is made by stereoscopic chest films taken of a cadaver in which the bronchi of both lungs have been injected with opaque bismuth paste. Since the advent of lipiodol injections into the bronchi the demonstration and study of the bronchi by this method have added complete confirmation of this classification and description. Furthermore from the start we have checked our roentgenographic findings accurately with the beautiful models and description of the bronchi by Birsch-Hirschfeld.[1]

The extent to which thoracic viscera may be dislocated by scar tissue is well known. But often we are not able to recognize the extent to which the lobes of the lungs are disturbed. The upper lobe is often contracted and foreshortened so as to lie entirely above the second rib, or the lower lobe may be so atelectatic and collapsed as to be hidden entirely behind the heart. Compensatory emphysema in the remainder of the lung allows it to fill the thorax. These changes may lead to serious clinical mistakes as to localization and extent of lesions, mistakes obviated only by competent roentgen-ray study of the bronchi with identification of the lobes.

The trunk markings seen in chest films are interpreted as being due to the bronchi. It is true that every trunk marking represents a bronchus, but these trunk markings are not produced by the bronchus alone. They are produced by the bronchus and the pulmonary artery, together with the lymphatic vessels and connective tissues around them. The pulmonary artery at the hilum on the right side lies below the bronchus to the upper lobe and on the left side above the main bronchus as it enters the lung. The pulmonary arteries can be visualized in these positions as they enter the lungs. Certain pathological changes cause dilatation and engorgement of the pulmonary arteries with consequent emphasis of the corresponding roentgenographic densities. Notably this change is found in emphysema. The increased translucency of the lung fields, the wider separation of the trunk markings and especially the accentuation of the pulmonary arteries speak for pulmonary emphysema. Within the lung the pulmonary artery follows the bronchus in all its divisions. It occupies a position slightly posterior and lateral to the bronchus.[2] Therefore, any condition which causes en-

gorgement, thickening or tortuosity of the pulmonary arteries will produce thickening of the trunk markings. This is notably true in mitral stenosis, congenital heart disease, or with any failing heart with consequent pulmonary congestion. Most striking are these findings in pulmonary sclerosis (Ayerza's disease).

Another anatomical point, important to understand thoroughly in order to evaluate and diagnose pulmonary disease, is the position of lymphoid tissue and the normal lymph flow in the lung. Large collections of lymph

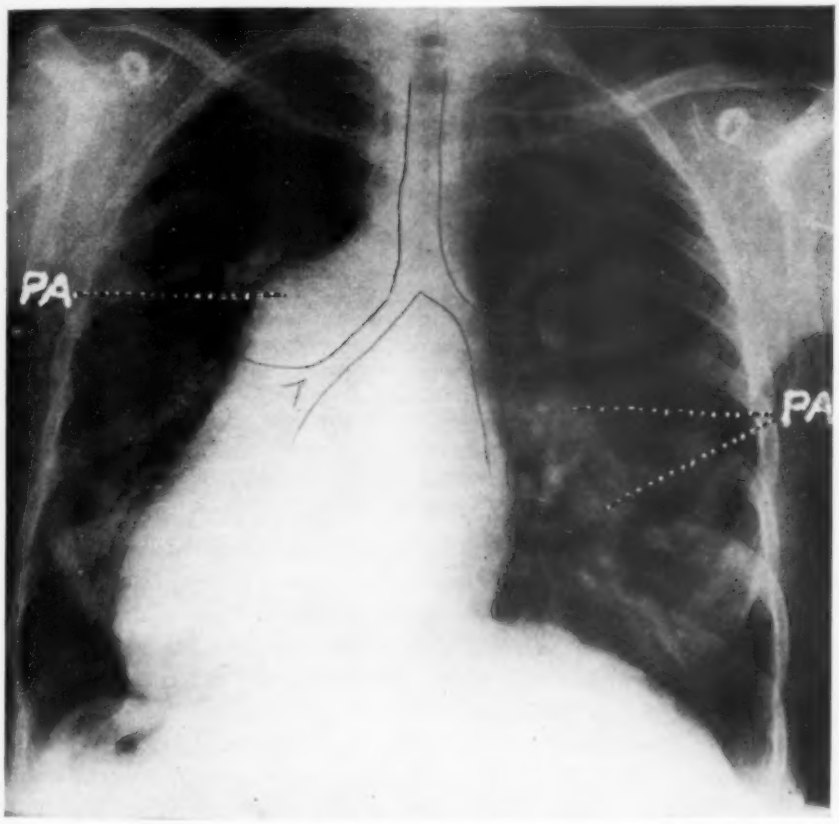

FIG. 2. Roentgen-ray of the chest of a case of congenital heart disease showing enlarged and thickened pulmonary arteries on both sides. Relationship to main bronchi is shown.

nodes are present at the bifurcation of the trachea and also in the hilum. Within the inner third of the lung, true lymph nodes are found along the bronchi in the angle at a bifurcation. Beyond the inner third of the lung we continue to find collections of lymphoid tissue but not anatomical nodes. In the lower lobes, however, the larger lymph nodes are found along the bronchi farther out than the inner third zone. Therefore, the trunk markings running into the lower lobes are normally heavier, are more studded,

and frequently more calcified. It is easy to overemphasize the significance of these studded heavy trunk markings. In such a condition as pulmonary Hodgkin's disease, a knowledge of the normal location of lymphoid tissue is of great aid in detecting the abnormal. The normal lymph flow in the lung is from the periphery of the parenchyma toward the hilum, except for a narrow zone beneath the pleura where the lymphatics about the veins drain toward the pleura. Infection is not carried by the lymphatics from the hilum out into the lung. Infection is carried by the lymphatics from the lung to the hilum. The bronchi, pulmonary arteries and pulmonary veins all have a rich supply of lymphatics accompanying them. Any acute respiratory infection, especially the exanthemata of childhood, may leave in its wake thickened trunk markings and enlarged pulmonary and hilum lymph nodes. The clinical significance of such findings in a child is of such importance as to have been the subject of a special investigation by a committee of the National Tuberculosis Association,[3] in order to standardize the interpretation. The report of this committee included the following paragraph:

> It was the consensus of opinion that children are probably more apt than adults to show definite x-ray evidence in the hilum and trunk shadows of simple as well as serious respiratory infections. Practically all children of the ages of those examined have had at one time or another one or more respiratory infections, especially measles, and whooping cough, that are likely to produce very apparent changes in the shadows mentioned and which will remain distinctly visible for a variable period of time. These apparent deviations from the normal are not necessarily abnormal when observed, but may be the harmless results of one or more infections. No doubt such appearances have many times been misinterpreted as evidence of tuberculosis.

The primary lobule, as described by William Snow Miller,[2] is a microscopic unit of the lung. Yet a thorough understanding of this anatomical unit, its structure and physiology is absolutely necessary for an accurate study of lung diseases. In consequence this unit must be brought into the mental picture when making a visual dissection and interpretation of lung disease by roentgen-ray examination. The primary lobule is that terminal division of the bronchus which includes the ductulus alveolaris and the air sacs connected with it, together with their blood vessels, lymphatics and nerves. At the end of the ductulus alveolaris, where the division into atria takes place, is the last point where we find lymphoid tissue and lymphatic vessels. Beyond this point in the atria, sacculae alveolaris, and alveoli, foreign material, organic or inorganic, is taken up and handled by the phagocyte. Any foreign invader, be it coal pigment or tubercle bacillus, which penetrates to this depth of the lung structure is engulfed by the phagocyte and deposited in the regional lymphoid tissue. Marked accumulation of phagocytes constitutes an exudate which may flood the alveoli and give the picture of pneumonia. This primary concept of inflammation in the anatomical unit is basic for diagnosis and study of lung disease by any method. Another point of interest and clinical significance is the arrangement of

smooth muscle at the end of the ductulus alveolaris. Here the smooth muscle ends in a thickened circular sphincter-like ring.[2] It seems logical to us to assume that in bronchial asthma with expiratory stridor the narrowing of the breathing tube takes place at this point where the sphincter-like muscle is present. This deduction awaits confirmation when studies of nerves and ganglia in the lung are more complete. We find some reason to attribute such action to this band of muscle because of our findings with lipiodol injections in pulmonary emphysema. In a normal lung, when lipiodol is injected into the bronchi and films taken immediately afterward, the air sacs are seen to be filled with the opaque oil and a rosette-like picture is given to the termination of the bronchi. In emphysema, however, the air sacs remain unfilled and the terminations of the bronchi stand out sharp and tapering. This observation is in direct contradiction to the findings and explanation of certain investigators in England. However, after checking this observation for three years, we are more and more impressed with its significance. Our deduction is that, as in bronchial asthma, the sphincter-like muscle narrows the entrance to the terminal air sacs and so impedes the entrance of the oil.

The secondary lobule is an arbitrary unit of the lung, accepted as being the amount of lung contained between two septa. These units, while they may be macroscopic, are not seen roentgenographically. Yet their influence on pathologic alterations in the lung is so great that a consideration of them is imperative. It is because of septa that sharply localized lesions are so often seen. Septa are prolongations of connective tissue from the pleura down into the lung. This connective tissue, rich in lymphatics, acts as an excellent barrier to the spread by continuity of any lung disease characterized by exudation. Inflammatory exudation, starting within any one of these small compartments between two septa will be definitely limited by these barriers. Spread through a septum will not take place until ulceration and cavitation occur. The restriction and localization of exudate by these septa explain the localized fan shaped densities on films in cases of pulmonary tuberculosis. The cellular elements of an acute lobular pneumonia or of an infarct are likewise held in check by these septa and consequently can give limited roentgenoscopic densities. Pulmonary new growths, however, are not checked by the septa, but continue to enlarge peripherally unrestrained by such barriers. Consequently the roentgen picture of pulmonary new growths is fundamentally different from that of inflammation.

The normal pattern of pulmonary anatomy having been established for roentgenoscopic study, it should be easy to recognize the abnormal. But to be able correctly to interpret the abnormal densities on chest films in terms of pathologic changes calls for understanding of the pathology and pathogenesis of lung diseases. Of prime importance are the fundamental pathological histologic changes that occur in the lung. These are congestion, exudation, infiltration, fibrous proliferation, caseation, calcification, ul-

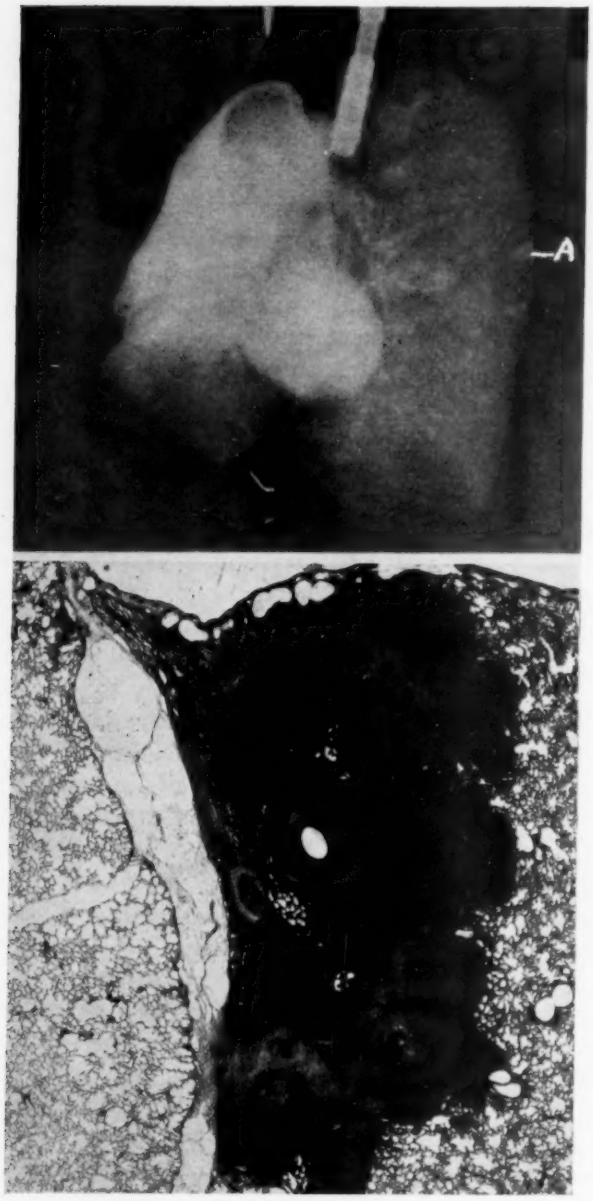

FIG. 3. *Above:* Roentgen-ray of the lungs of a case of pulmonary tuberculosis. *A* Triangular shaped localized density seen on roentgen-ray lung films indicating caseation. *Below:* Microscopic section through block *A* showing tuberculous caseous bronchopneumonia occupying a whole secondary lobule limited by septa.

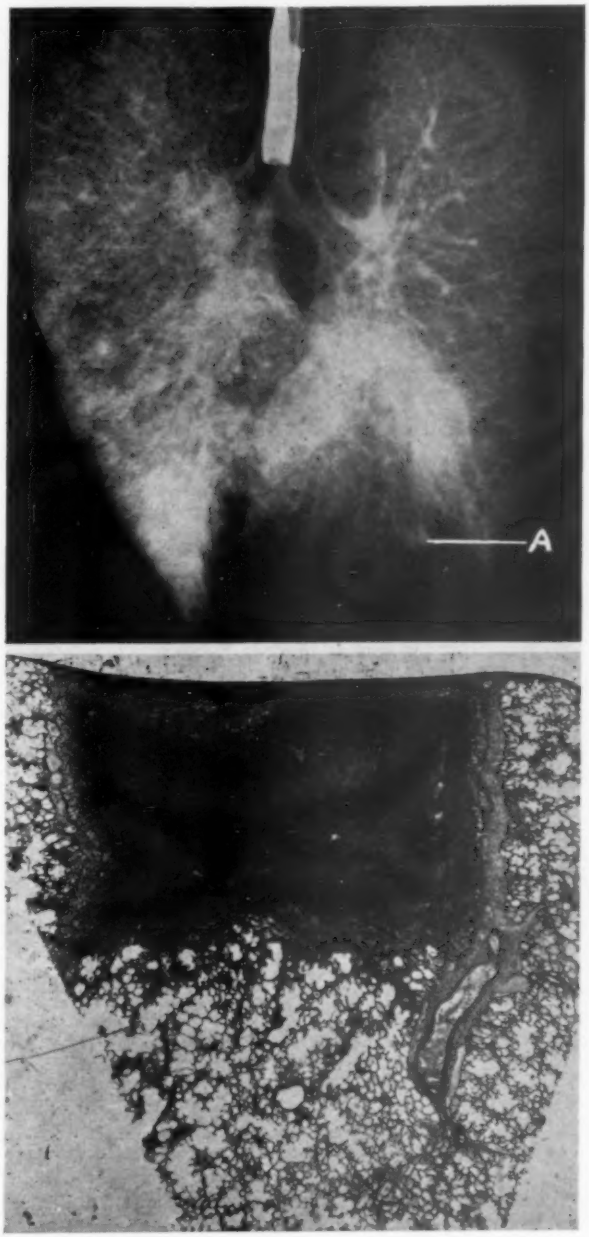

FIG. 4. *Above:* Roentgen-ray of the lungs of a case of mitral stenosis showing general thickening of all bronchi. *A*. Limited density beneath diaphragmatic pleura indicating exudate and infiltration.

Below: Microscopic section through block *A* showing hemorrhagic infarct limited by septa.

ceration, and cavitation. Accordingly it is necessary to determine the type and quality of density produced on a film by each of these changes. This has been done by years of observation. The interpretation of the abnormal densities seen on chest films and on films taken of lungs removed from the body, has been carefully checked by postmortem studies. The procedure for the postmortem studies is to remove from the body the lungs and trachea intact. After removal, the lungs are inflated to normal size and stereoscopic films are then made of them. These films are then studied and the interpretation recorded. The lungs are properly fixed and preserved for later gross and microscopic pathological study. In the earlier work serial sections of various types of lesions in tuberculous lungs were made for an accurate study of pathological anatomy, as a check on the roentgen-ray findings. At the Hamilton County Tuberculosis Sanatorium it still remains a routine procedure to preserve and study all lungs after this method. The gross dissection of the lungs is made along the bronchi as previously described in order accurately to localize the lesions in relation to the divisions of the bronchi. The gross pathological findings are recorded and representative blocks of tissue are removed for microscopic studies. The microscopic pathological diagnosis is then added to the record. Finally we have the clinical history and findings, the chest films, the postmortem lung films, and the gross and microscopic postmortem findings all recorded for critical review. The films have all been interpreted in terms of anatomical localization and pathological changes. The check-up is precise. During the 20 years of such study, although most of the material has been that of pulmonary tuberculosis, we naturally have encountered many examples of other chronic lung inflammation, such as abscess, bronchiectasis, fungus infections, syphilis, and new growths. These studies have taught us that the quality of the densities on the films produced by the various tissues and their abnormal changes, vary from the least to the heaviest quality as follows: 1. Cavity. 2. Normal lung parenchyma. 3. Exudate. 4. Cellular infiltration. 5. Fibrous proliferation or scar tissue. 6. Caseation. 7. Calcification. These comparative values of roentgen-ray densities and pathological histologic changes in the lung constitute the ground work for study of lung pathology.

The etiological diagnosis of the alterations visualized and described in the lungs must needs be amplified from our knowledge of the pathogenesis of the various lung diseases. It is of course, obvious that roentgenoscopy has distinct limitations in the exact etiological diagnosis of diseases. Lobar or bronchopneumonia can be diagnosed and localized with accuracy in terms of pneumonic exudate but the causative organism must be determined by clinical laboratory methods. Abscess or bronchiectasis can be demonstrated but the diagnosis must be completed by bacteriological and clinical studies. It must be remembered also that each or both of these conditions may be concomitants of other lung diseases such as new growths, gumma, pneu-

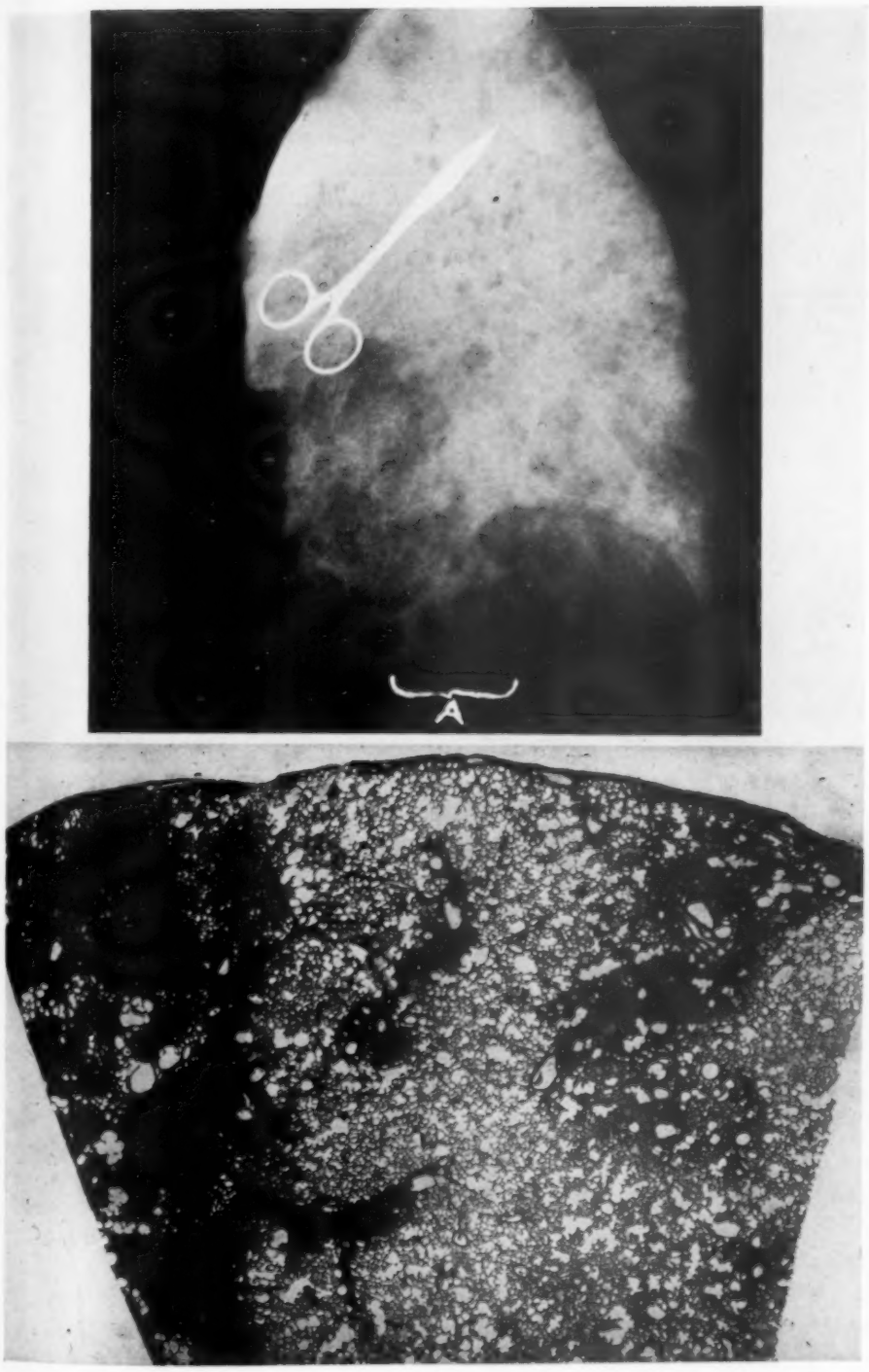

FIG. 5. *Above:* Roentgen-ray of the lung of a case of pulmonary tuberculosis. *A.* Interesting area along diaphragmatic border showing three differing densities. The heaviest zone represents caseation. The middle zone is comparatively normal. The third zone represents exudate.

Below: Microscopic section through block *A* showing three distinct tissue changes. The heaviest change represents caseous bronchopneumonia; in the middle is seen normal lung; on the other side is seen acute bronchopneumonia.

monia, tuberculosis or various other chronic lung infections. Frequently, however, the roentgen-ray picture of lung disease is sufficiently characteristic to portray with greater positiveness the etiology of the disease. Pulmonary tuberculosis can be studied and diagnosed with great accuracy by roentgenoscopy. This is very fortunate because in the study of any chronic lung disease, the first point to decide, if possible, is whether or not the condition is tuberculosis. If one understands and applies a knowledge of the pathogenesis of pulmonary tuberculosis to its roentgenologic study, one has accurate and ample means of recording its progressive changes. Tuberculous infection is not static. It is a moving or dynamic process subject to constant change, and it is this progressive or dynamic change that demands positive roentgenoscopic recognition. First of all the primary type of infection is universally recognized. This is a clinical demonstration in the human of a phase of Koch's phenomena in the animal. On the films we see and recognize the caseous or caseo-calcareous lymph nodes in the hilum; the Ghon focus [4] represented by a caseous, fibrous, or fibro-calcareous nodule in the lung; the heavy trunk markings connecting the Ghon focus to the hilum and all this portraying the primary complex of Ranke.[5] This record of past events is seen in the average adult chest. The quantity or lack of calcium in the lung and hilum may roughly measure the degree or amount of infection the individual has suffered. The adult apical type, sometimes called bronchopulmonary phthisis, is always the result of secondary infection. It represents the reaction to infection in an allergic soil. The reaction takes place out in the parenchyma of the lung where, exposed to roentgenoscopic view, it is subject to the most accurate diagnosis. The first response to the implantation of the tubercle bacillus in allergic soil is outpouring of exudate. This mononuclear exudate, accompanied by proliferation of fixed tissue cells, leads to the characteristic microscopic picture of tubercle formation with giant cells, caseation, epithelioid cells and lymphocytes. From this point the disease progresses either to the reparative changes of fibrosis and calcification, or to the destructive changes of ulceration and cavitation. At any stage before the development of fibrous tissue proliferation, absorption of exudate can take place.

OUTLINE OF PATHOLOGICAL CHANGES OF ADULT APICAL TYPE PULMONARY TUBERCULOSIS

1. exudate
2. tubercle
3. caseation

absorption . fibrosis calcification ulceration cavitation

As previously described, the early exudate is walled in by the septa of the lung which produces the localized fan shaped densities seen on films. This form of pulmonary infection spreads by bronchogenic or so-called intracanalicular route. In general, the course of tuberculosis is apt to be intermittent with periods of exacerbation and remission, which correspond to recurrent discharges of infection. The pulmonary lesions of an adult type are the result of repeated infections either exogenous or endogenous. This leads to multiple lesions in the lungs in different stages, of progressive and changing character. Each lesion produces a corresponding characteristic density on the roentgen-ray film depending upon the histological structure of the lesion, exudative, caseous, fibrotic or calcified. Thus on the films one may visualize densities of variable quality and by proper interpretation piece them together into the dynamic pathological picture of pulmonary tuberculosis. Lymphohematogenous or post-primary type, recently so thoroughly reviewed and brilliantly emphasized by Dr. James Alexander Miller,[6] is graphically recorded in localization and pathological changes in terms of exudation, proliferation, fibrous tissue and calcification. Miliary tuberculosis is understood and recognized by its uniform distribution of characteristic small lesions. The basal types of caseous lobar or bronchopneumonia offer the greatest difficulty of diagnosis. The pathologic changes can be recognized but the etiological diagnosis is uncertain. Such types are particularly frequent in the negro and in that race should be more often suspected. Serial stereoscopic chest films in pulmonary tuberculosis stand as a record of the progressive pathologic changes and offer an opportunity to study, and accurately to diagnose the pathogenesis of the disease.

Summary

By study of stereoscopic chest roentgenograms, the normal and pathological anatomy of the lungs can be visually dissected. Most important in the medical or surgical treatment of any lung disease is complete and accurate localization of the lesions. Localization of the lobes and lesions is made possible through accurate knowledge of the bronchi and all their divisions. The position of blood vessels and lymphoid tissue must be considered and applied in roentgenoscopic studies of the lungs. The part played by the anatomical units of the lung in the pathological changes of disease must be understood. All of these factors which make up the normal stereoscopic pattern, influence the recognition of the abnormal densities. The interpretation, however, of these abnormal densities in terms of tissue changes, demands an understanding of the pathology and pathogenesis of lung diseases. The quality of the roentgenoscopic densities produced by the various tissues and their abnormal changes are described. Pulmonary tuberculosis in its various forms can be studied and diagnosed with great accuracy by means of stereoscopic roentgenograms. The progress of the disease either toward healing by absorption of exudate, formation of fibrous scar tissue,

or spread of exudate and destruction of lung by ulceration and cavitation is demonstrated. A method of accurate control of the roentgenoscopic diagnosis by pathological studies is described.

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CARDIAC OUTPUT IN COMMON CLINICAL CONDITIONS, AND THE DIAGNOSIS OF MYOCARDIAL INSUFFICIENCY BY CARDIAC OUTPUT METHODS *

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The heart is an organ with but one function. Its function is to pump the blood; it does nothing else. For this reason we have a clearer understanding of the heart than of any other organ. We can make pumps; but who can manufacture a working model of any other viscus? One can consider the heart's function in much the same way as one would consider the performance of any man-made pump.

There is no need to present the details of the methods available for measuring the amount of blood pumped by the heart, the cardiac output. All these methods are too technically difficult for general utility. There is no satisfactory way of estimating their absolute accuracy, so it is safest to regard them as inaccurate. When the better methods are applied to patients the standard deviation of duplicates from the mean is about 10 per cent.[14, 19] But this is not cause for too much pessimism. Not long ago the different methods gave a totally different average level of cardiac output, and repeated estimations on the same subject were most divergent. Now we are far past that stage. Numerous series of normal young adults in the basal condition, examined by a number of the best modern methods, have been reported. Although these methods differ profoundly in construction and technic the averages obtained by each agree surprisingly well. The agreement of duplicate estimations has been greatly improved also. We have come a long way. Perhaps, compared to the accuracy of the data on which clinicians must base their decisions, we are not so badly off.

The time has come when clinicians should have a working knowledge of the results these methods are yielding. For either cardiac output and cardiac work are of fundamental importance, or our present conceptions of many diseases of the heart and circulation are completely erroneous. Therefore it is of interest to collect and survey the trend of results secured by the methods most worthy of confidence. One must discard from such a compilation a large number of results obtained by methods whose accuracy, in the light of modern knowledge, is doubtful. It is also safer to exclude the results secured by certain investigators who, though they used a satisfactory method, did not give satisfactory evidence that they had mastered the difficult technic. It also seems better to omit results obtained by methods which, while probably accurate enough in themselves, so disturb the subject that it seems probable that the apprehension, excitement, or actual pain en-

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tailed would change the cardiac output of certain patients from the true basal level.

Results Obtained by Cardiac Output Methods

The data which have been included may be divided into three groups: first, the results of studies of the cardiac output of normal persons; second, the results secured in clinical conditions common enough to provide a respectable series of cases; and last, the results in the less usual types of disease in which only a few, or perhaps only a single subject has been available for testing.

First let us consider the results obtained on normal individuals. They may be summarized as follows:

(1) There is a definite level of basal cardiac output characteristic for each subject and analogous to the basal metabolic rate. This level is roughly related to the size of the subject.[6, 19] Some subjects have a very constant basal cardiac output, others are much more variable.[19]

(2) Like the basal metabolic rate the basal cardiac output is elevated in adolescence and apparently tends to decline after 50 years of age.[19]

(3) The average cardiac output in the standing position is somewhat smaller than that in the horizontal position. The sitting position gives an intermediate result.[1, 4, 15]

(4) The cardiac output is raised from the basal level by taking food, by drinking large amounts of water, by exercise, and by excitement.[2, 6, 17] Extremes of environmental temperature will alter it also.[2, 6, 13, 17] Note the similarity between the situations mentioned in the foregoing statement and those long known to induce attacks of angina pectoris.

Before discussing the results obtained in disease it should be pointed out that cardiac output methods yield erroneous results on certain types of patients. This must be explained in more detail.

The best of the modern cardiac output methods are based on the inhalation of gases foreign to the body and gaseous equilibrium between the lung air and blood must take place or the results will be in error. This equilibrium can be demonstrated to exist for normal persons, but when the lungs are primarily diseased, or secondarily affected by cardiac decompensation, there is a strong possibility that it may not take place. Furthermore adequate mixing of inhaled gases, required by some methods, cannot be assumed when the lungs are abnormal. Therefore workers in this field have to make a choice. Either they avoid the field of pulmonary disease altogether, or they attempt to demonstrate the principles fundamental to their method in the diseases in which they are interested. The difficulty with the latter procedure is just this: no two patients ever being exactly alike, the demonstration that the method is applicable should really be made on every patient. But when one deals with single experiments the inherent errors are so large and so hard to evaluate that, in a certain proportion of cases, they might readily yield results providing a false sense of security. Therefore,

while interesting work is being done in this difficult field we do not hesitate to say that we have not full confidence in the results obtained and, therefore, they will be omitted from further consideration at this time.

The results obtained in clinical conditions, without pulmonary involvement, and common enough to permit securing a considerable series of subjects, will be considered first. Let us pay attention only to the average of the results, for this will go far towards making unimportant the inaccuracies of method, and minimizing the effect of the random fluctuations so often seen in patients. Therefore in compiling table 1, the averages only have been used. The figures can be found in the literature; we wish only to call attention to their trend.

TABLE I

Clinical Conditions in Which Considerable Data Are Available

Average basal cardiac output per min. related to body weight or surface.

Increased in	Hyperthyroidism [2, 6, 19, 21] Anemia [2, 6, 19, 21] Fever (experimental) [2, 6, 13]
Essentially *unchanged* in	Intercurrent disease not affecting the heart or circulation [19] Hypertension [2, 6, 19] Hypotension [19] Angina pectoris (between attacks) [19, 20] Coronary thrombosis (after recovery from acute symptoms) [19, 20, 21] Valvular heart disease (when well compensated) [6, 19, 20, 21] Auricular fibrillation (when well compensated) [19, 20]
Diminished in	Cases recovered from cardiac decompensation [18, 19] Neurocirculatory asthenia [18, 19]

As is shown in table 1, the average cardiac output is definitely increased in hyperthyroidism, anemia, and in fever induced experimentally by typhoid vaccine or diathermy. There are no adequate data on the cardiac output in the febrile diseases.

The average cardiac output is unchanged in both hyper- and hypotension. It is unchanged in the common non-febrile diseases, diabetes, neoplasms, neuroses, gastric ulcer, etc., as would be expected. More surprising is the fact that it remains normal in the presence of certain serious diseases of the heart indicated in table 1.

On the other hand the average cardiac output is diminished in patients who have once suffered from congestive heart failure even though they have recovered from decompensation when the test is made. This result is consistent with clinical knowledge that recovery from decompensation is not complete. More unexpected was the finding that the average cardiac output in neurocirculatory asthenia was distinctly subnormal. The many symptoms which these patients share with those having serious cardiac disease may well have a common origin in this diminished circulation.

The trend of the results, obtained in conditions either rarer clinically or more difficult to secure for an estimate of cardiac output, are given in tables 2 and 3. Because of the instability of the cardiac output of certain subjects and the large errors still inherent in the best methods, we have no

confidence in the results of single estimations and have not included data of this kind. The disease conditions shown in tables 2 and 3 have been studied well enough to deserve attention, although we are by no means sure that further work will show them to be truly representative of the groups to which they belong. The number of patients tested in each group is given in brackets following the data. It is to be emphasized that this number is often very small.

TABLE II

Acute Clinical Conditions in Which but Few Data Are Available

(The change recorded is in relation to the value obtained during the patient's more normal periods. The bracketed figure gives the number of cases studied in each instance.)

Basal cardiac output per min. related to body weight or surface.

Increased in
- Acidosis (experimental) [12] (1)
- Angina pectoris (during attack) [20] (3)
- Arteriovenous anastomosis (the comparison is with data obtained after occlusion of the anastomosis manually and by operation) [8] (1)

Diminished in
- Artificial pneumothorax (certain cases) [3] (2)
- Paroxysmal auricular fibrillation (during attack) [19] (1)
- Paroxysmal auricular tachycardia (during attack) [18, 19] (3)

Table 2 shows the trend of the results in certain acute clinical conditions which, either because they were not permanent, or because they were brought about by the observer, permitted tests to be made on the same patient both in the abnormal and in the more normal condition. Therefore the change recorded is in relation to the same patient's more normal periods.

These data (table 2) deserve brief comment. The results obtained in angina pectoris indicate that increased cardiac work is an essential feature of the attack in the patients studied. This is consistent with the conception that this increased work, by creating a demand for blood which diseased vessels cannot supply, results in anoxemia of cardiac muscle which causes pain. Were angina pectoris caused primarily by spasm of coronary arteries one would expect that cardiac output would be unchanged or diminished during the attack. But the paucity of data and the difficulties of getting satisfactory estimations of cardiac output under conditions of cardiac pain must be emphasized. These patients described their pain as an ache. No estimations of cardiac output have been reported during the agonizing pain characteristic of the more spectacular forms of angina.

While careful work has demonstrated that in certain cases artificial pneumothorax is followed by a reduced cardiac output, in other cases no change has been demonstrated.

Paroxysmal tachycardia was accompanied by a marked diminution of cardiac output in three cases, but in one case, in which duplicate estimations were not made, no change was detected.

Table 3 gives the trend of the results in more permanent conditions, and the change indicated is in relation to data obtained in normal persons. The field covered is extensive, and limitation of space permits emphasis of only a few points.

TABLE III

Chronic Clinical Conditions in Which but Few Data Are Available

(The change recorded is in relation to data obtained on normal persons. The bracketed figure gives the number of cases studied.)

Basal cardiac output per min. related to body weight or surface.

Increased in	Aortic regurgitation (well compensated) [1, 5, 19, 21] (8)
	Coarctation of aorta [7] (1)
Essentially *unchanged* in	Addison's disease (not in shock) [19, 20] (3)
	Aortic regurgitation (well compensated) [1, 5, 19, 21] (12)
	Portal cirrhosis of liver [19, 20] (2)
	Acute endocarditis [19] (5)
	Heart block (congenital) [2] (1)
Diminished in	Advanced mitral stenosis (well compensated) [21] (4)
	Aneurysm of the aorta [19, 20] (6)
	Auricular flutter [20] (1)
	Heart block (acquired, complete) [19] (2)
	Hypertension (certain cases with small hearts) [18, 19, 20] (8)
	Myxedema [19, 20] (2)
	Pick's syndrome [11, 21] (5)

The increased cardiac output found by four authors in certain cases of well compensated aortic regurgitation is unexpected enough to deserve attention. Perhaps it should be thought of in connection with the demonstration by Sir Thomas Lewis [9] that peripheral vasodilatation is present in certain cases of this disease. If there is general vasodilatation and the blood pressure remains unchanged, an increased cardiac output becomes a logical necessity, and these results are a demonstration of this point of view. But it must be remembered that only about one-half of the reported cases show this increase.

The diminished cardiac output found in certain cases of hypertension demonstrates a type of compensation which needs emphasis. By reducing its output the heart can maintain a high blood pressure without doing more work than normal. This is doubtless the reason for the absence of cardiac hypertrophy in certain cases of hypertension. Most cases of hypertension have enlarged hearts and, the cardiac output being normal, the heart's work is increased.

ON THE DIAGNOSIS OF MYOCARDIAL INSUFFICIENCY

Now let us leave the field of description and ask ourselves some questions concerning the possibility of diagnosing myocardial disease by means of cardiac output methods. At first thought one would expect that patients with bad heart muscles would have a smaller cardiac output than normal persons. But the problem turns out to be far more complicated than this. Most workers in this field are agreed that the basal cardiac output, related to the patient's weight, or surface area, cannot be used to decide whether an individual's heart muscle is diseased or not. Although the averages differ, many individuals with every evidence of serious myocardial disease have cardiac outputs which are at or even above the normal average. Obviously the body bends every effort to maintain the cardiac output at a level sub-

servient to the body's needs. If we are some day to use these methods to detect myocardial disease we must look elsewhere than at the basal cardiac output per minute referred to the size of the body.

Our problem, therefore, is first to understand myocardial disease; when we understand it thoroughly, its detection should be easy. One can think of the heart as a pump and, to get the problem clearly before us, let us consider a simple man-made pump standing over a well. Were such a pump to perform badly, and were one to apply medical methods of diagnosis, one would listen learnedly over the valves with a stethoscope, and would attach wires to various parts and attempt to draw conclusions from the deflections of a galvanometer, the "electropumpogram." But certainly these methods would leave much to be desired and all of us would proceed more directly to quantitative measurement. Our first thought might be to measure the length of time it would take to fill a bucket with water, to ascertain the normal output, and to compare the performance of our pump with it.

But there are difficulties with this simple method of procedure. A man comes to his well, and labors with the pump handle as usual, but he is rewarded by a miserable trickle of water. He suspects that the pump is out of order. He is entirely wrong. The well is going dry. The pump cannot function unless water is conducted to its inlet, neither can the heart pump blood unless the latter is delivered to it by the veins. A small output is not compelling evidence either of a broken pump or a diseased heart. The profession has often gone wrong on this point. When, in acute infection, the circulation begins to fail how often has our therapy been directed at the pump whereas the trouble is more often analogous to the well going dry.

One other fundamental conception can be best explained by another homely example. Our friend attaches the garden hose to his pump. While he puts his usual effort into the handle, his wife, to play the stream upon the farthest flower bed, tightens the nozzle. Now the stream squirts higher and farther than before, but it has been reduced in volume, it takes longer to fill the bucket; the pressure has increased, the output decreased. Therefore the pump's output is in part dependent on his wife's adjustment of the nozzle, and the cardiac output is likewise in part dependent on changes in the caliber of the arteries. But, as long as he labors with constant effort on the pump handle, one attribute of the flowing stream is practically independent of his wife's adjustments; this is the product of output times pressure, i.e. the work. His wife has it in her power to increase the pressure, but in so doing she diminishes the output; the product, output times pressure, remains the same, no matter how she adjusts the nozzle, within reasonable limits. Similarly changes in the peripheral circulation can change the output, but the work is a function of the heart alone. Obviously the work of the heart is more likely to be of service in indicating the heart's condition than is the output.

Let us next consider the behavior of the heart under certain experimental conditions analogous to those which have been mentioned. The late Pro-

fessor Starling devised an animal preparation for studying the heart and the experiments were first performed by him and his associates.[16] Figure 1 shows a typical result. You constrict the out-flow tube. Suddenly meeting increased resistance the heart fails to empty as completely as before. The same amount of blood flows in during diastole, the chamber enlarges and the muscle fibers are stretched and, like other stretched muscles, the heart begins contracting with more vigor, the circulation is restored with the heart larger and working harder than before.

If, on the other hand, one constricts the inlet tube the heart does not fill

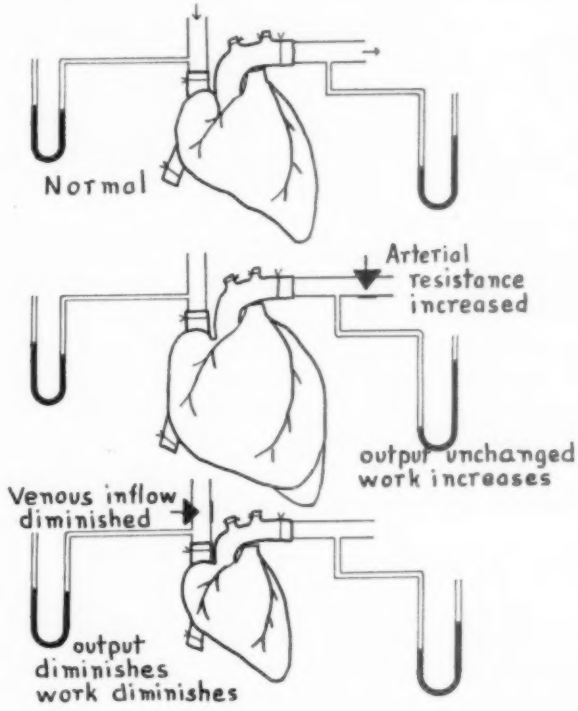

FIG. 1. "The work of the normal heart per beat is a function of its size." Diagram illustrating the type of evidence on which Starling's "Law of the Heart" was based. To avoid confusion, the lungs and the other apparatus essential to Starling's Heart-Lung Preparation have been omitted.

as well during diastole. It therefore gets smaller and when equilibrium is attained we have a smaller heart doing less work. Starling pointed out that under all these conditions the work of the heart per beat was proportional to its size and this principle has since been known as Starling's "Law of the Heart." When the heart begins to fail the law does not hold, for the heart gets larger instead of smaller as its work decreases.

Now by means of cardiac output measurements and the ordinary blood pressure estimations one can roughly estimate, in patients, the largest part

of the heart's work, that performed by the left ventricle. The size of their hearts can be estimated by roentgen-rays, preferably using the orthodiagraph. One can calculate left ventricular work per beat and heart volume and see where the results lead.[19]

We have a series of well over 250 cases.[19, 20] One can separate out a group characterized by the fact that there is no suspicion of cardiac disease in any. Otherwise they are very divergent, including normal persons, persons suffering from diseases not affecting the circulation primarily: tumors, neuroses, diabetes, etc. Also those with diseases affecting the circulation but not, in the instances chosen, the heart: hyperthyroidism, anemia, hyper- and hypotension. Let us look for relationships which hold under these diverse circumstances. Out of this maze of data comes the fact that the relationship which holds most closely is that described by Starling. The work of the normal heart is related to its size. Data obtained in a wide diversity of clinical conditions agree with results obtained in experiments with the isolated heart and lungs of the dog. We have a right to believe, therefore, in the wide applicability of this conception.

Figure 2 illustrates this relationship.[19] The dots, representing the values obtained on persons without cardiac disease, arrange themselves along the line AB, and are bounded by the lines CD and EF. The circles represent the values obtained on persons who were once decompensated, so we know that they have myocardial disease. They obviously occupy a different place on the chart. Not only can one conclude that under normal conditions the work of the heart per beat is a function of its size but one also can say that, in hearts known to be abnormal, this law does not hold.[19] Here, then, is a method which has the promise of identifying hearts with abnormal myocardia.

But it must be realized that this method has its limitations. Cases of coronary disease cannot be detected by the relationship of heart work to heart size. Perhaps the amount of heart muscle affected is ordinarily too small a proportion of the total to be detected in resting patients. But this line of thought gives promise of permitting the detection of the myocardial dysfunction characteristic of that great group of cases whose end is congestive failure.

Perhaps you now expect us to give you instructions how to find the heart's work and size on your patients. We cannot do so. Cardiac output estimations are laborious and technically difficult. The recent improvements in our method have greatly increased the speed but have increased the complexity of apparatus. We see no means of simplifying our technic. So we cannot present to you the logical conclusion of our research, a simple practical method for the estimation of myocardial function. Indeed we do not believe that our primary aim should be to attain such a method. It should be to shed so much light on the problems of myocardial function that the signs and symptoms available to every physician will take on new meaning, and thus permit more accurate estimations of the condi-

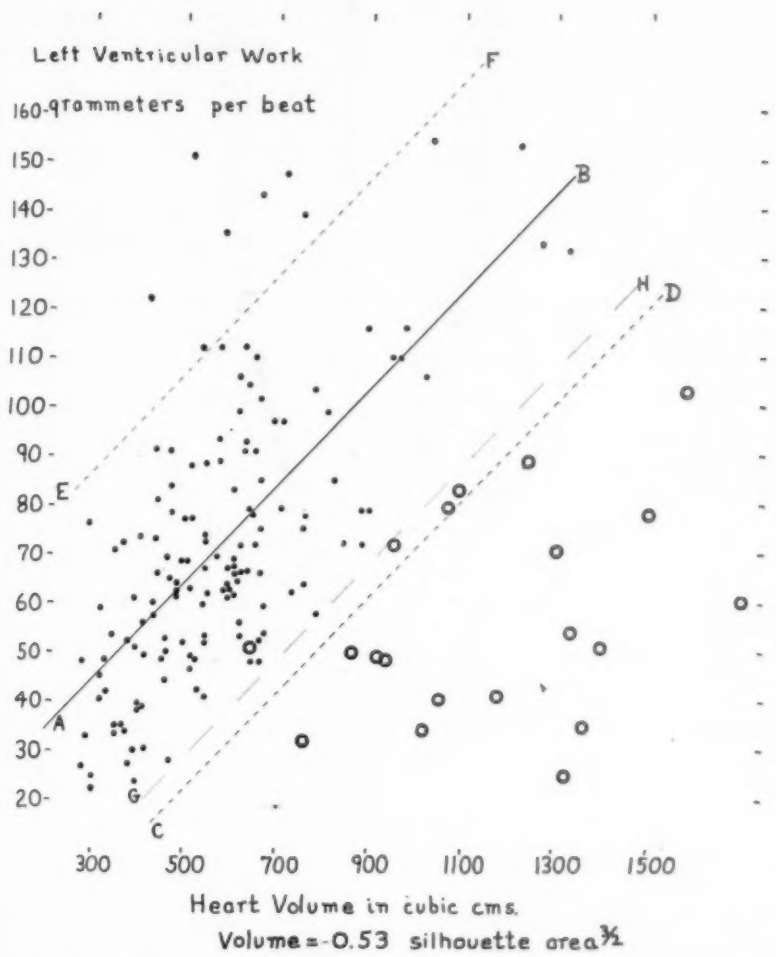

FIG. 2. Evidence that the "Law of the Heart" holds for clinical conditions, and can be used to detect cases with abnormal myocardial function. Each symbol represents the average of duplicate estimations of basal cardiac work. The *dots* indicate the values obtained on normal persons and patients without evidence of cardiac disease. The *circles* indicate values obtained on persons who formerly had cardiac decompensation; they had regained compensation by the time the estimations were made. The dots arrange themselves about the line AB whose position has been calculated from the data. The positions of CD and EF were likewise obtained by statistical methods; their distance from AB is twice the standard deviation of the data. Therefore if any result falls to the right of CD the probability of its being abnormal is about 97.5 in 100. GH is the line, parallel with AB, which most cleanly divides the dots from the circles and so it may be thought of as the lower limit of the normal zone. (Reprinted by permission of the *Journal of Clinical Investigation*).

tion of the heart with resulting improvement in the prevention and treatment of its diseases.

When our data are searched with this in mind many things are found which throw light on clinical problems. One may be emphasized here. A moderate increase in size of the heart may be physiological. In the few

conditions in which heart work is ordinarily increased, hyperthyroidism, hypertension and anemia, a moderate increase in heart size is not necessarily an indication of myocardial dysfunction. But, in general, in all other conditions, increased cardiac size is the best objective sign of myocardial weakness and it deserves all the emphasis that clinicians have long put upon it.

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STUDIES ON THE INCREASED METABOLISM IN HYPERTHYROIDISM *

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Baltimore, Maryland

The metabolic phenomena characteristic of hyperthyroidism are common to both the clinical and the experimental forms. In the clinical disease, these changes may only be observed en masse. They may be measured only as they are reflected in the *total* displacement of certain equilibria such as the oxygen consumption, carbon dioxide production, glucose tolerance, nitrogen balance, and the creatine metabolism.

Experimental hyperthyroidism may be produced in animals to any desired degree by the administration of thyroid extract or by the injection of thyroxine. Under these circumstances it is possible to analyze the metabolic alterations and to subject various elements thereof to quantitative chemical examination. By analogy, at least, the results of such observations are applicable to the clinical disease.

In the light of accumulated experience these metabolic effects have been more and more accurately described and defined. Their appearance is delayed by an interval (15 to 24 hours) corresponding to the latent period characteristic of the action of thyroxine. They are not dependent upon the integrity of the nervous system.[1] Experiments conducted in vitro suggest that the effect of thyroxine is restricted to intact cells; upon minced tissue it is ineffective.[2] Of particular significance is the fact that, once established in the intact animal, certain metabolic changes persist in representative tissues after isolation from the body.

For example, if an animal receives thyroid extract by mouth or thyroxine by injection there ensues a series of phenomena quite analogous to those observed in clinical hyperthyroidism: nervousness, weakness and fatigability, tachycardia, hyperglycemia, loss of weight and increase in the basal metabolic rate. If the heart is removed from such an animal and is artificially perfused, it continues to beat for hours at a rate conspicuously more rapid than those of the untreated control animals. This persistent tachycardia indicates that the action of thyroxine survives the isolation of the tissues or organs. It has been fully described and analyzed elsewhere.[3] It suffices to point out here that this effect is uninfluenced by iodine or iodides.

* Read at the Philadelphia meeting of the American College of Physicians, April 29, 1935.

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† Under a Fellowship of the National Research Council, Washington, D. C., and a Jacques Loeb Fellowship and a Bingham Fellowship of the Johns Hopkins Hospital and University, Baltimore.

Observations upon the oxygen consumption of tissues isolated from an hyperthyroid animal have demonstrated considerable and constant increases, in comparison with tissues of normal controls. Typical curves are shown in figure 1. Samples of the cells of the kidney, liver and diaphragm of thyroxinized animals consume oxygen at rates conspicuously in excess of those of similar tissues from normal animals. Such effects have also been demon-

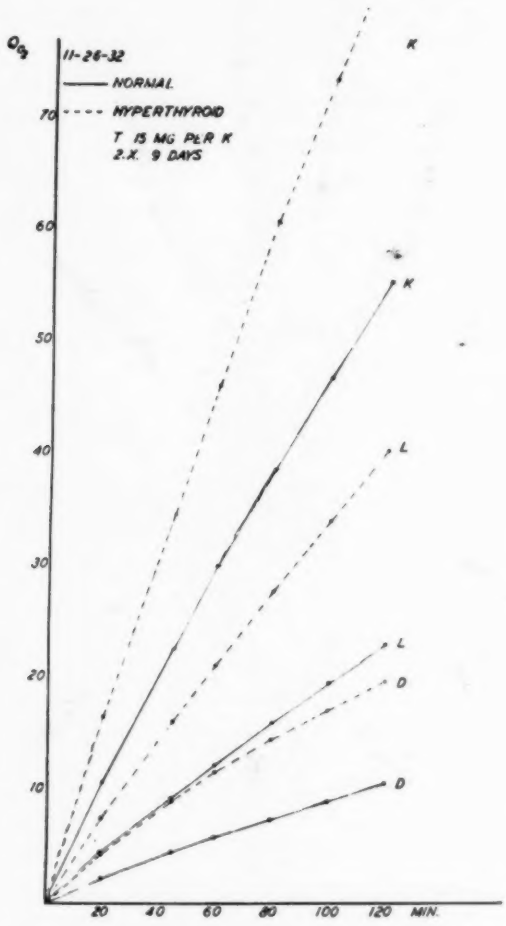

FIG. 1. Typical curve of oxygen uptake by tissues from a normal and from an hyperthyroid animal.

strated in other cells as diversified as those of the spleen, heart, nerve, and lung. Moreover, similar and commensurate increases of tissue respiration have been observed following the production of the hyperthyroid state by injection of anterior pituitary extract containing the thyreotropic hormone.[4]

Like the tachycardia of the surviving heart, the augmented oxygen utilization of the isolated tissue is uninfluenced by iodine. Studies have been

made in an effort to analyze this effect of thyroxine, to compare the increased increment of respiration with other phases of cellular metabolism and with the respiration of normal tissue.

In the first place the authors have examined the theory that this increased oxygen consumption is secondary to the effect of thyroxine upon the metabolism of carbohydrate. Meakins [5] has summarized the important aspects of the carbohydrate metabolism of muscle as related particularly to circulatory failure. There is abundant clinical and experimental evidence that in

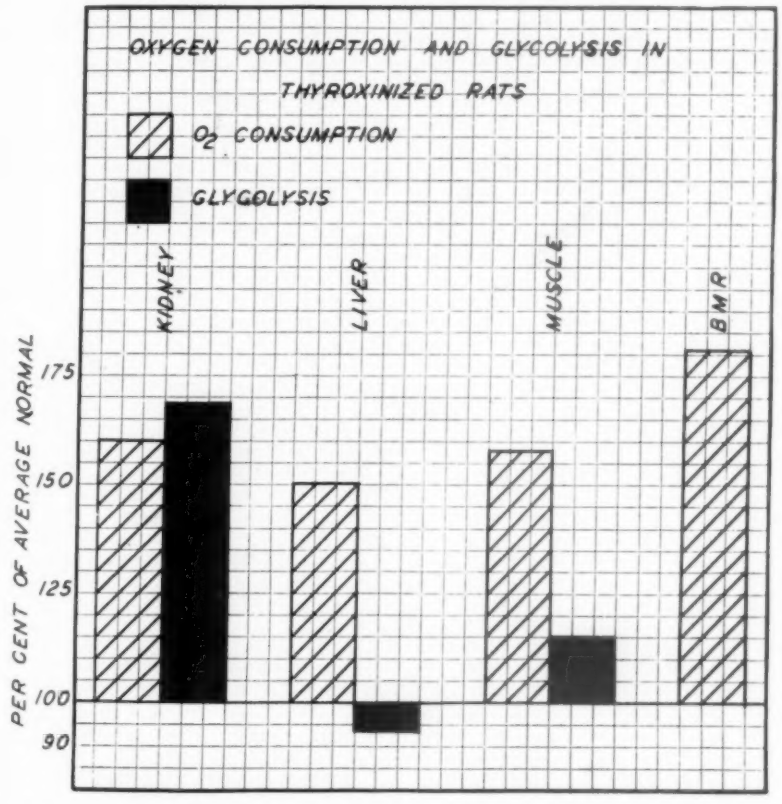

FIG. 2. Comparing the basal metabolic rate with the oxygen consumption and glycolysis in surviving tissues of thyroxinized rats.

hyperthyroidism this phase of metabolism may be profoundly affected: the glycogen stores are depleted and, under conditions which normally lead to its production, lactic acid accumulates in the blood. The demand for oxygen to bring about the oxidative removal of excessive amounts of lactic acid has been supposed to explain the increased oxygen consumption characteristic of hyperthyroidism.[6]

Experiments calculated to test this theory have been reported elsewhere.[7, 8] In brief summary: it has not been possible to protect animals

from the metabolic effects of thyroxine by the administration of substances —sodium fluoride and moniodoacetic acid—which interfere, at various stages, with the breakdown of carbohydrate to lactic acid. Furthermore, while the augmented oxygen utilization persists in the tissues of the hyperthyroid animal after isolation from the body, a commensurate increase of carbohydrate breakdown can be demonstrated only in the case of kidney tissue. (Figure 2.) It is therefore to be concluded that the increased

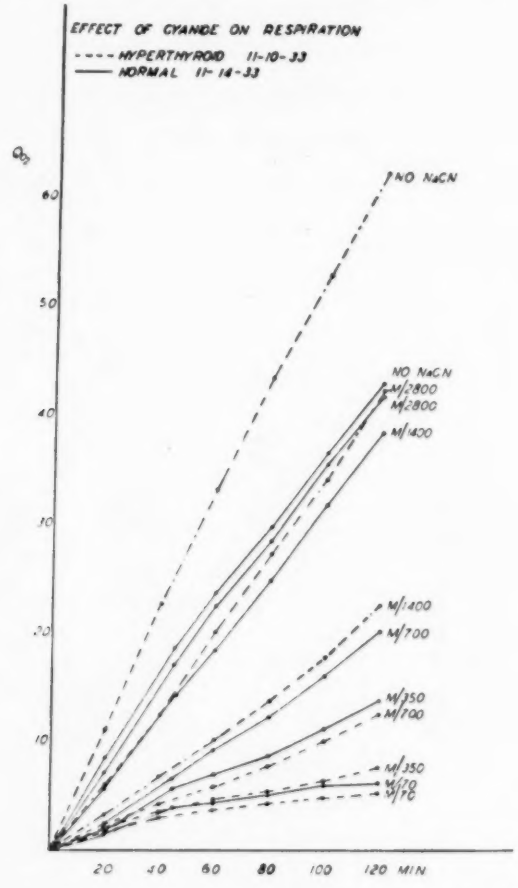

FIG. 3. Oxygen consumption of kidney tissue from normal and thyroxinized rats in various concentrations of sodium cyanide.

oxygen consumption in hyperthyroidism is not primarily due to an augmented carbohydrate metabolism.

The extra increment of respiration in the tissues of the thyroxinized animal has been compared to the respiration of normal tissues in its reaction to the influence of cyanide. The normal tissue respiration may be almost completely inhibited by this substance.[9, 10] It has been demonstrated that the increased oxygen consumption induced by thyroxine is likewise sensitive

to cyanide. Indeed it may be inhibited by cyanide in concentrations which produce little or no effect upon the oxygen consumption of normal tissues. The results are summarized in figure 3 which depicts the oxygen utilization of kidney tissue from normal and thyroxinized rats in various concentrations of sodium cyanide. In M/2800 solution the curves nearly coincide.*

Finally, it has been possible to show that the effects of thyroxine persist, not only in the isolated tissue of an animal to which it has been administered but in an aqueous enzyme-containing extract thereof. Normal muscle tissue contains a powerful enzyme soluble in water and capable of

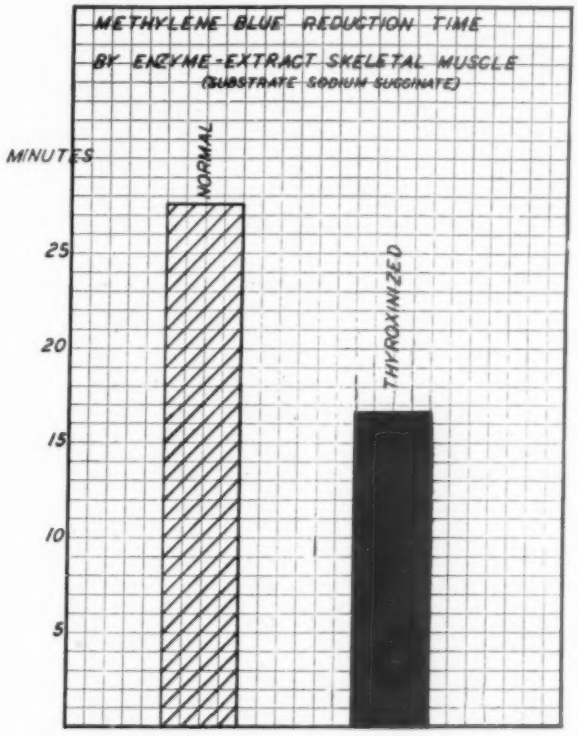

FIG. 4. Indicating increased enzymatic activity in the aqueous extract of muscle from thyroxinized rabbits.

dehydrogenating succinic acid to fumaric acid in the presence of a suitable hydrogen acceptor. Methylene blue may act as such an acceptor, becoming decolorized in the process, and the rate of its decolorization serves as a measure of the speed of the reaction. Aqueous extracts have been prepared from muscle tissue of normal and of thyroxinized animals and have been compared by means of this reaction. The average time required for decolorization of the dye by the enzyme extracts from normal animals' tissues was greater by 60 per cent than those from the thyroxinized animals (figure

*This does not imply that cyanide may be used with benefit to inhibit the primary metabolic action of thyroxine. Its effect is upon a mechanism vital to the cell.[11]

4). It appears that, as regards this example of tissue enzyme, under the influence of thyroxine it is increased in amount or potency.

In certain fundamental respects, then, the action of thyroxine upon tissue metabolism survives the isolation of the cells from the remainder of the organism, or even in substances extractable from such cells. Conversely, the effects of thyroid insufficiency also become inherent in the tissue cells, and are manifest in vitro in the *decreased* activity of certain enzymes.[12] It is to be assumed that the thyroid secretion is indispensable among the factors which preside over the normal metabolism of the tissues. Abnormality may result in case of excess or deficiency.

These observations may be offered in explanation of certain features of clinical hyperthyroidism (thyrotoxicosis). This syndrome combines the manifestations of an excess of thyroid secretion with the events which lead to that excess. The production of exophthalmos, so long regarded as distinguishing clinical hyperthyroidism (Graves' disease) from the experimental form, has recently been accomplished by Marine.[13] It is, apparently, an accompaniment of events which, in addition, lead to the augmented secretion of the thyroid substance.

It is to be concluded that the effects of thyroxine upon the patient with hyperthyroidism include the metabolic phenomena demonstrable in the isolated tissue in the experimental disease. These effects are undoubtedly widespread and involve, perhaps to varying degree, the cells of all the metabolizing tissues in the body. The primary result is an increase in the metabolic requirements of each tissue. These are collectively manifest in the increased utilization of oxygen by the patient at rest, and in loss of weight unless the daily caloric intake is considerably raised. It is probable, too, that the excessively rapid heart beat is, in part, an expression of the effect of thyroxine upon the metabolism of the cardiac muscle.

Moreover, there may ensue, perhaps secondarily, an impairment of the integrity of tissues or organs. Functional insufficiency may result in any tissue whenever the physiological demands upon it approach or exceed the limits set by its own metabolism. The occurrence of congestive heart failure and of angina pectoris in hyperthyroidism clearly exemplifies such imbalance. The relief of angina pectoris by thyroidectomy, in the presence or absence of hyperthyroidism,[14] is no doubt due as much to the resultant lowered metabolic requirements of the heart muscle as to the decrease in the circulatory load. The relief by thyroidectomy of arteriosclerotic gangrene in an elderly patient with hyperthyroidism, observed * on the Medical Service of the Johns Hopkins Hospital, is almost certainly due to the consequent reduction in the demands of the tissue to meet the available blood supply.

These observations contribute nothing directly to the therapy of hyperthyroidism. It is to be emphasized that none of the metabolic phenomena which survive in the isolated tissue are abated by iodine. In this sense the

* To be reported.

results confirm the opinion, recently reaffirmed by Means and Lerman,[15] that the beneficial effect of iodine in hyperthyroidism is exerted upon the gland itself with consequent diminution of its secretion. For the present the treatment of the metabolic phenomena must be directed toward the reduction of the amount of circulating thyroxine.

Summary

The metabolic effects of thyroxine, produced in animals, survive in the tissues after isolation from the body and in substances extractable from such tissues. Analysis of these effects indicates: (1) that the metabolism of many varieties of cells is augmented; (2) that the activity of certain tissue enzymes is increased in the process; and (3) that these effects are not inhibited by iodine. By analogy it is suggested that the metabolic phenomena of clinical hyperthyroidism include those demonstrated in the experimental type. It is emphasized that the beneficial effect of iodine upon the clinical disease is primarily upon the thyroid gland and only secondarily upon the metabolic phenomena resulting from the excessive thyroid secretion.

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STUDIES RELATING VITAMIN C DEFICIENCY TO RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS; EXPERIMENTAL, CLINICAL, AND GENERAL CONSIDERATIONS *

I. RHEUMATIC FEVER

By JAMES F. RINEHART, M.D., *San Francisco, California*

ON the basis of experimental data previously reported [1, 2] the concept was presented that rheumatic fever may be the result of the combined influence of vitamin C deficiency and infection. It is the purpose of this communication briefly to review this and to summarize further confirmatory experimental observations and other data accumulated during the past three years that would appear to support this thesis.

Experimental Method. The methods employed are essentially similar to those reported.[1, 2] Guinea pigs were maintained on a basic diet adequate in all food factors except vitamin C. Regulating the intake of vitamin C by giving small measured amounts of orange juice, the animals were maintained for varying periods of time in acute and subacute or chronic states of vitamin C deficiency or scurvy. In the original observations the infecting agents used were various strains of a beta hemolytic streptococcus, which cause spontaneous lymphadenitis in guinea pigs. In the subsequent work other organisms have been used including a gamma type streptococcus and *B. bronchosepticus,* also derived from spontaneous guinea pig infections. The experimental work has included a study of the pathological effects of acute, subacute and chronic scurvy alone, of similar degrees of scurvy combined with infection and, as controls, infected and non-infected animals maintained on the same basic diet adequately supplemented with orange juice. Inasmuch as pathological findings are in essential agreement with those previously reported, they may be briefly summarized and illustrated.

With respect to the rôle of infection, it may briefly be said that in the presence of adequate vitamin C nutrition, rheumatic type lesions have not been observed. When superimposed on vitamin C deficiency, essentially similar observations have been made with the several infecting agents used. It would appear, however, irrespective of the precise organism used, that a high degree of virulence favors the development of significant pathological changes. Further, in the conduct of the experiments it has become quite apparent that the defense mechanism of the vitamin C deficient animals is less effective, and that the ability to localize the infecting organism is impaired.

* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935.

This work has been made possible by research funds granted from the Christine Breon Fund for Medical Research.

The second and final part of Dr. Rinehart's article will be published in the December number of the ANNALS.

Lesions in the Heart Valves

In uncomplicated vitamin C deficiency, definite atrophic and degenerative changes occur in the collagenous stroma of the heart valves. In scurvy with superimposed infection, striking lesions of a combined degenerative and proliferative character develop in the heart valves with considerable frequency. These lesions present many basic similarities to the early lesions of rheumatic fever. Poynton and Schlesinger [3] have pointed out that the valvular vegetations owe their formation to subendothelial proliferation of cells and not to a primary destruction of the endothelium. Ribbert [4] speaks of characteristic changes in the subendocardial tissues beneath the thrombus or beneath the free surfaces, consisting in an enlargement of and gradual increase in the number of cells whose cytoplasm enlarges and consequently causes a mild thickening of the tissues. This change, he finds, is accompanied by a transformation of the "*zwischen-substanz*" which becomes clearer, more translucent, and the fibrillar structure less distinct. Clawson [5] too has noted the essentially proliferative character of the inflammatory process in rheumatic fever. The accompanying illustrations will serve to

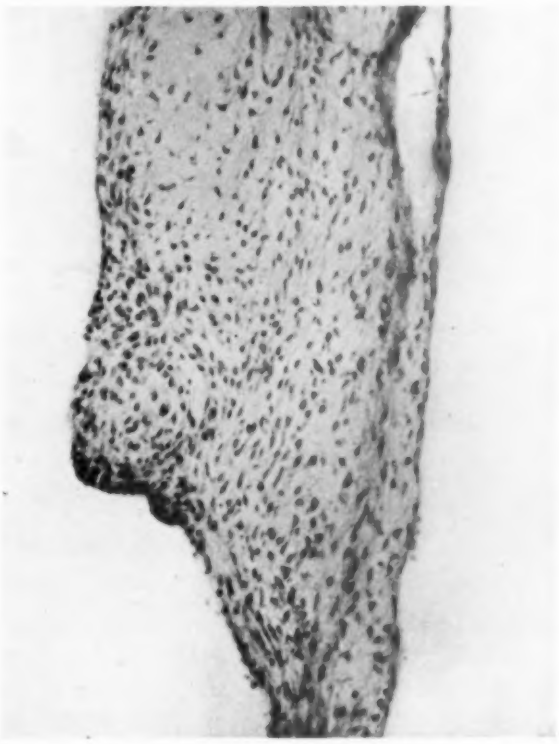


Fig. 1. Mitral valve; scurvy plus infection (gamma streptococcus). Showing diffuse swelling of the valve substance, impoverishment of collagenous stroma and an early proliferation of the stroma cells, just beneath the contact surface. × 90.

show the character of the experimental lesions and their basic similarity to those of rheumatic fever.

Figure 1 shows a moderate diffuse interstitial proliferative reaction in the mitral valve in an animal subjected to scurvy and an experimentally induced lymphadenitis due to a gamma type streptococcus. This lesion is an example of the milder type and corresponds closely to Ribbert's description of the early rheumatic valvulitis. In figure 2 is shown an intense prolifera-

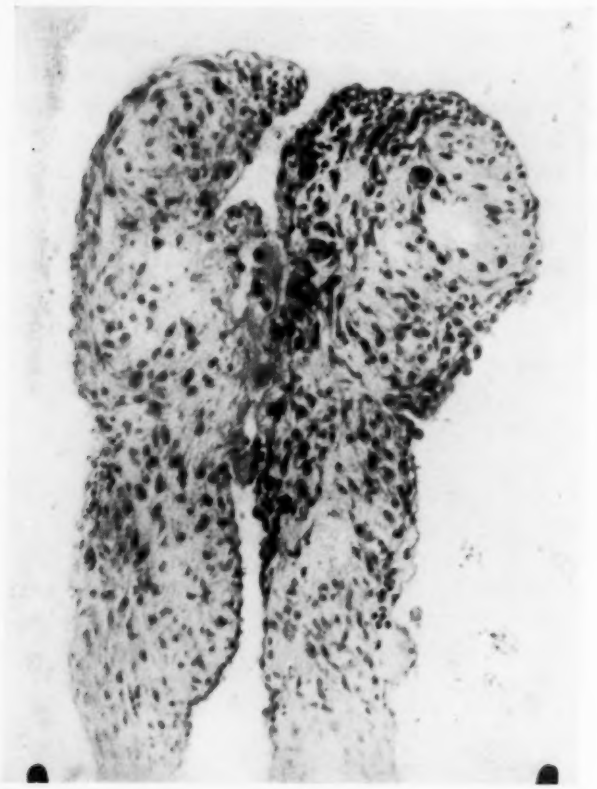
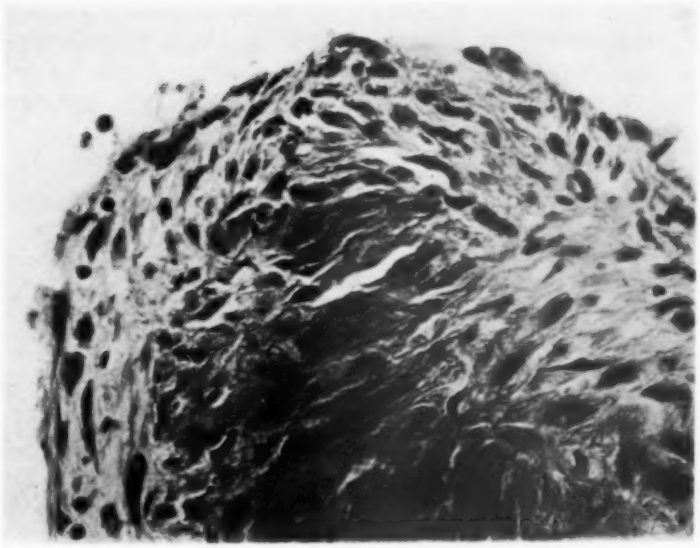
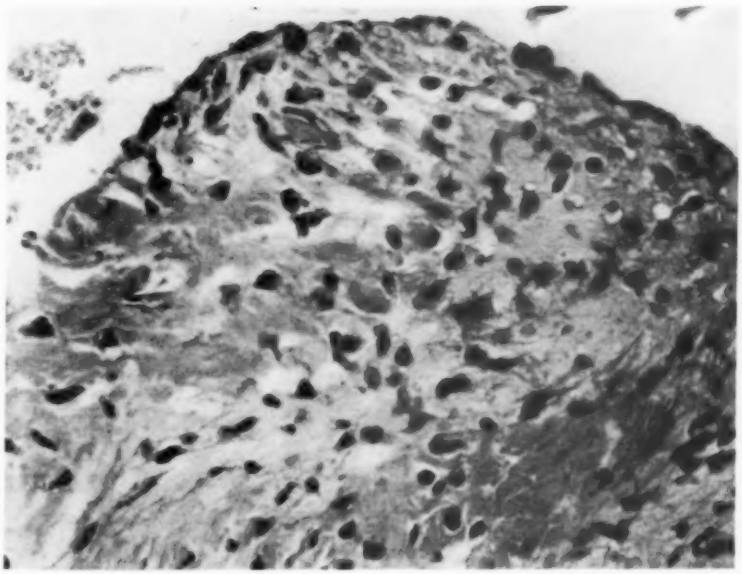


FIG. 2. Aortic valve; subacute or chronic scurvy plus infection (beta streptococcus). A striking proliferative reaction in two leaflets of the aortic valve. The normal regular collagenous stroma is gone. Large hyperplastic cells actively proliferate in an edematous stroma. Fragments of an unidentified hyaline material are present in the substance of the valve. The endothelial lining of the contact surfaces is interrupted and a thin film of fibrin merges with the underlying valve substance. × 120.

tive lesion in the aortic valve that occurred in an early experimental series in which an acute local infection due to a beta type streptococcus was superimposed upon the scorbutic state. The rather intense proliferative reaction in two leaflets of the aortic valve is shown. Fragments of an unidentified hyaline substance resembling swollen collagen are present in the substance of the valve. The endothelial lining of the contact surface is interrupted and a thin film of brilliant fibrin merges with the valve substance in this





FIGS. 3 and 4. Figure 3 (above) shows a typical early rheumatic verrucous endocarditis. Figure 4 (below), an experimental lesion in an animal subjected to acute scurvy with superimposed infection (beta streptococcus). The striking similarity of the two lesions is apparent. In each instance, a peculiar hyaline substance and an associated cellular proliferation constitute the verrucous nodule. Approximately × 450.

region. The proliferating cells showing hyperchromatic nuclei and an abundant dully eosinophilic cytoplasm correspond closely to the reactive cells of rheumatic fever. The remarkably close resemblance that the experimental endocarditis may bear to that of rheumatic fever is shown in figures

3 and 4. Figure 3 is a characteristic verrucous lesion of rheumatic fever.* This and the experimental lesion (figure 4) show a hyalinized material within the valve substance which with the associated cellular proliferation constitute the verrucous nodule. The experimental lesion was produced in this instance by the combined influence of a relatively acute scurvy and infection with a beta streptococcus.

The pathological changes encountered in the heart muscle are less strik-

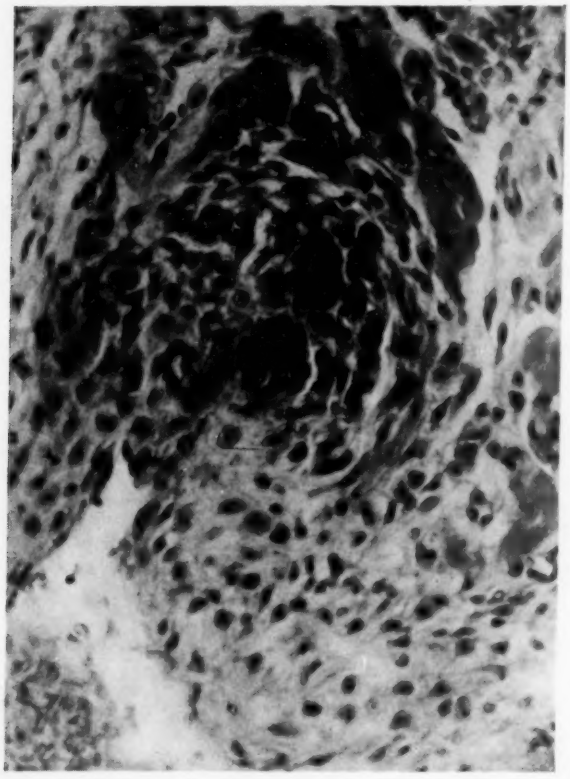


FIG. 5. A concentric large cell proliferative reaction in the endocardium adjoining the heart muscle near the angle of attachment of the mitral valve. Relatively acute scurvy plus infection (subcutaneous) with *B. aërtrycke*. Similar lesions have been seen with other infecting agents when combined with vitamin C deficiency. The general character of the lesion as well as the individual cytoplasmic and nuclear characters of the cells recall the Aschoff reaction of rheumatic fever. × 400.

ing than the valvulitis described. However, proliferative reactions are not infrequently seen in the heart muscle, beneath the endocardium and in the pericardium which are considered fundamentally similar to the Aschoff reaction. Figure 5 shows a local proliferative reaction which was found at the angle of attachment near the base of the mitral valve. The con-

* This photograph, used to illustrate a typical rheumatic endocarditis by Dr. Clawson,[5] was kindly furnished by him and is published with his permission.

centric lesion is composed of large hyperchromatic connective tissue cells. The general arrangement and cellular constituents are much like those in the Aschoff body. Figure 6 shows one of a number of nodular proliferative reactions that have been seen in the pericardium of experimental animals. In a few instances the "fibrinoid" degeneration of Klinge [6] has been noted in the heart muscle. However, experimentally this change is much more frequently seen in the articular tissue.

It would appear that the more delicate connective tissue supportive structure of the guinea pig heart might account for the less striking interstitial reactions.

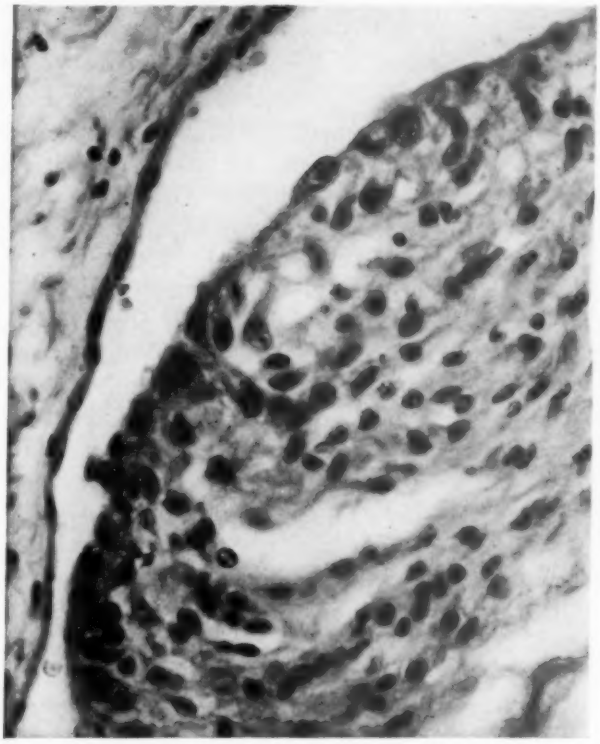


FIG. 6. A localized proliferative reaction in the pericardium. Subacute scurvy plus infection (gamma streptococcus). × 500.

PATHOLOGY OF THE JOINTS

An early manifestation of vitamin C deficiency in the guinea pig is an arthropathy characterized by pain, tenderness, and swelling of the joints. The detail of the relationship of vitamin C deficiency to joint pathology is best reserved for the subsequent section dealing with arthritis. However, it may be said that the essential changes encountered in and about the joints [2] in subacute scurvy with or without infection correspond closely to those

described by Klinge and Grzimek [7] in careful pathological studies of the lesions in the arthritis of rheumatic fever. The occasional occurrence in the experimental animals of subcutaneous nodules is of great interest. This finding, too, will be discussed in the consideration of the scorbutic arthropathy.

General Considerations

The Problem of Hemorrhage. It is usual to think of scurvy as a disease characterized by the occurrence of widespread hemorrhage. It is true that hemorrhage is commonly encountered in vitamin C deficiency due to impairment of the intercellular substance supporting capillaries. However, the degree of hemorrhage seen is dependent to a great extent upon time factors and the intensity of the deficiency. Hemorrhagic manifestations in rheumatic fever are of more frequent occurrence than it is generally considered. Poynton and Paine [8] have described blood stained synovial fluid in rheumatic arthritis. Chester and Schwartz [9] have noted the rather frequent occurrence of purpuric lesions on the skin of the legs and arms in rheumatic fever and consider this as a clinical evidence of recurrent activity of the disease. A recent study of Coburn [10] would indicate that hemorrhage is characteristic of the acute phases of rheumatic fever, noting that " in all patients dying during marked activity of the rheumatic process, hemorrhagic lesions were widespread." In cases of sepsis, hemorrhages are of course common but as pointed out by Coburn [10] the hemorrhages of rheumatic fever cannot be assigned to sepsis. A scorbutic factor in rheumatic fever would appear to offer a statisfactory explanation for the hemorrhagic manifestations of the disease.

Similarities of the Fundamental Pathology of Scurvy and Rheumatic Fever. Certain fundamental considerations would strongly favor the concept that vitamin C deficiency may play a rôle in rheumatic fever. The histological studies of Aschoff and Koch,[11] Höjer,[12] Wolbach and Howe [13] have demonstrated that the scorbutic animal is not able to form normal intercellular cement substances. Collagen is of course the most widely distributed intercellular substance in the body. Höjer [12] emphasized the occurrence of degenerated or imperfectly formed collagen even in early and relatively mild degrees of scurvy. It is apparent that the heart valves and peri-articular tissues are sites in which connective tissue substances are subjected to greatest stress. It would be here then that the first evidence of an inadequacy would become manifest. Klinge [6] in careful studies of the histopathology of rheumatic fever emphasizes the importance of a peculiar alteration seen in connective tissues which he has called a " fibrinoid " degeneration. This he considers the initial and characteristic lesion of rheumatic fever. The exact interpretation of this change is not entirely clear. It is my opinion that in some instances it represents an imperfect collagen intimately associated with fibrin derived from blood plasma exuded from regional capillaries. Regardless of the exact nature of the " fibrinoid "

degeneration, a seemingly identical lesion is seen in the experimental animals, particularly in the tissues about the joints and less commonly in the heart muscle.

Discussion

It is believed that the experimental work reported offers strong evidence that vitamin C deficiency in conjuction with infection may operate as an important factor in the etiology of rheumatic fever. Experiments conducted over a period of years have given essentially consistent findings. Supportive experimental data have been published by Stimson, Hedley and Rose.[14] The possibilities of the experimental approach, however, have in no way been exhausted. Among other things the minimal degree of vitamin C deficiency which with infection will produce significant lesions, has not been determined. Further, the pathology corresponding to that of a *chronic* rheumatic endocarditis has not been produced. The mode of operation of the factor of infection has not been determined. In the majority of instances we have seen no evidence of bacterial localization in the proliferative endocardial lesions. However, in one instance large numbers of bacteria were seen directly associated with such a lesion. We do not know whether the infection acts through the mechanism of a toxin or through localization of small numbers of organisms which evade detection. It is considered very significant, however, that a variety of infecting organisms in adequately nourished animals have in no way produced comparable "rheumatic type" lesions.

Epidemiological Considerations

An analysis of the known epidemiology of rheumatic fever would appear to strengthen the concept reported. In fact, careful scrutiny of clinical and epidemiological data has not only afforded nothing contradictory but rather has given confirmatory evidence. It would appear that the known predisposing factors in rheumatic fever, which are considered below, could be explained on the basis of vitamin C deficiency.

Malnutrition and Rheumatic Fever. Numerous observers have called attention to the frequent association of malnutrition with rheumatic fever. Vining [15] emphasized the malnourished state of the pre-rheumatic child and suggested the existence of vitamin B deficiency. Campbell and Warner [16] agree that it is the debilitated child that develops rheumatic fever. Swift [17] observes that most rheumatic children appear undernourished. McLean [18] found 82 per cent of rheumatic children underweight for their height. Certain symptoms which include fatigue, loss of appetite, loss of weight, muscle pains, and nervousness are common to both latent scurvy and to the pre-rheumatic or early rheumatic state. A mild anemia is another finding common to the two conditions.

Geographic Distribution. Rheumatic fever is a disease of the temperate zone. Clarke [19] has drawn attention to its practical absence in the tropics. The natural dietaries in the various sections of the tropics are well supplied

with anti-scorbutics and scurvy is rarely encountered in the tropics except under unusual circumstances as those that sometimes prevail in labor camps or military campaigns. The observations of Sir Leonard Rogers [20] are of particular interest. Speaking of India, he states "heart diseases were half as common as in London and rheumatic endocarditis was quite absent although streptococcal infections were otherwise as frequent." The comparative rarity of rheumatic fever and rheumatoid arthritis in Holland has been pointed out by van Breeman.[21] The importance of truck gardening and the dairy industry in Holland suggests that the dietary might be more than usually adequate in vitamin C-containing foods.

Social Incidence. The social incidence particularly suggests an environmental factor in the etiology of rheumatic fever. Campbell and Warner [16] find rheumatic disease the most crippling affection of the poor. Swift [22] notes that statistics show obvious rheumatic fever is 15 to 20 times more frequent in the laboring classes than in those forming the bulk of private practice. Glover [23] believes the true incidence of rheumatic fever in England to be directly proportional to the degree of poverty and estimates the occurrence of acute rheumatism is 20 or even 30 times as great in the poor as in the well-to-do. It would seem to the writer that a disease with such an amazingly dominant incidence in poorer people could not be explained on the basis of a specific bacterial infection or on the basis of recurrent non-specific respiratory infection alone. Some fundamental environmental factor would appear to lie in the background.

Age Incidence. Acute rheumatic fever is in the main a disease of childhood. The maximum incidence of first attacks occurs between the ages of five and twelve. This is a period of active growth in which the nutritional requirements are great. It has recently been shown [24] that children of elementary school age require approximately twice as much vitamin C per kilo for the prevention of latent scurvy as is needed by adults.

Urban Incidence and Familial Tendency. The higher incidence of rheumatic fever in cities would appear explainable on the basis of greater liability to respiratory infection and, for the poorer classes, less adequate nutrition. Similarly the basis of the high familial tendency might lie in a common unhealthy bacterial and nutritional environment.

Seasonal Incidence. Suggestive evidence of a possible relation of latent scurvy and rheumatic fever is present in the concurrent seasonal incidence of the two diseases. All authors are agreed that the greatest incidence of rheumatic fever in this country is in the late winter and early spring. This is a season following a period of diminished availability of fresh fruits and vegetables in which scurvy either latent or manifest would be expected to occur.

The Rôle of Infection in Rheumatic Fever

A consideration of the rôle of infection in rheumatic fever has been summarized in a previous publication.[2] A factor of infection would appear to

be thoroughly established. A specific infecting agent has not been established. Streptococci of various types have been implicated. Recent studies [25, 26] have pointed to a beta hemolytic streptococcus as the common offender. However, infection alone does not appear to afford an adequate explanation of the disease. Coburn [25] has stressed the occurrence of a wave of upper respiratory infections preceding the development of a lesser wave of rheumatic fever. Only a small minority of those suffering the infection develop rheumatic fever. It would appear that some mechanism renders this smaller group susceptible to the disease. It is the author's concept that this mechanism is a state of latent or sub-manifest scurvy. The writer wishes to make it entirely clear that the factor of infection in rheumatic fever is in no sense minimized. Clinical data as well as the experimental studies indicate the importance of infection in this disease. Beta hemolytic streptococci, perhaps because they are the most common cause of acute upper respiratory infections, are probably the most important associated organisms. Further, the experimental work does not preclude the possible influence of allergic factors. Indeed the work of Sulzberger and Oser [27] indicates that moderate vitamin C deficiency favors the development of hypersensitivity to neoarsphenamine. A latent scurvy might likewise favor the development of bacterial hypersensitivity.

The Existence of Latent Scurvy

The recognition of latent deficiency states has offered a problem of considerable difficulty. Until recently the approach to the problem of latent scurvy has been largely through indirect evidence. A method of definite but limited value for the detection of vitamin C deficiency is afforded by the determination of the capillary strength. Using this method as a criterion, Göthlin [28] found evidence of vitamin C undernutrition in about 18 per cent of the school children (between 11 and 14 years) in the province of Uppland (Sweden) during the months of April and May. Dalldorf [29] similarly using capillary resistance tests, considers that a mild degree of vitamin C deficiency may constitute a problem of considerable public health importance. A recent survey of food purchases of families on relief [30] in a California city revealed some striking and unexpected data. It was found that purchases of vitamin C-containing foods in a high percentage of cases fell far below the standard considered necessary for adequate nutrition. To quote from the study: "If the choice of food in a California market, in the middle of summer when the variety of fresh fruits and vegetables is at a maximum and the cost at a minimum, shows this deficiency, what is to be expected of other localities during the winter months is appalling."

The recent chemical identification of vitamin C has stimulated extensive researches that promise rapid progress in our knowledge. Yavorsky, Almaden and King,[31] in titration of extracts of tissues obtained post mortem, found that "latent human scurvy, generally unobserved in clinical practice,

is fairly common." Of 31 cases under 10 years of age, four were in a range so low that latent scurvy was clearly evident. Of 36 cases over 10 years of age, six showed critically low vitamin C content of tissues indicating a depletion nearly as severe as found in terminal human or guinea pig scurvy. The evidence derived from clinical, nutritional, and chemical studies then all points toward the existence of latent scurvy.

Storage, Utilization and Depletion of Vitamin C

The ability of the body to store vitamin C is limited. The rapid elimination of large quantities of vitamin C after ingestion, and the continued loss from the body without a dietary source being supplied, has been shown by Harris, Ray, and Ward.[32] Practically nothing is known with respect to factors which may hinder or prevent absorption or utilization of vitamin C. There is a certain amount of indirect evidence that achlorhydria may increase the basic requirement.[33] Factors which may deplete stores of vitamin C are of great interest and probably of great importance. Our own experience from experimental observation is that certain infections may act in this way. Dry [34] states that scurvy may be precipitated by infective febrile illnesses. Harde and Benjamin [35] have presented brief evidence that infection may deplete the organic stores of vitamin C. Van Eekelen and Kooy [36] have shown that fatigue may operate in a similar fashion. Studies of factors conditioning absorption and causing organic depletion of vitamin C are of great importance and should be extended. If acute infection depletes the organic store of vitamin C, it is of great importance to the concept presented in this paper. Under such circumstances a mild grade of deficiency might by infection be rendered significantly severe in a relatively short period of time. It would appear that such a mechanism might explain the latent phase noted by many observers between the acute respiratory infection and clinical onset of rheumatic fever.

Clinical Studies

During the past 18 months a clinical approach to the problem has been made in association with Dr. Amos Christie in the Childrens' Cardiac Clinic of the University of California Medical School.[37] Although the duration of the study is not considered long enough to be conclusive, many interesting data have been collected. The general method of study has included dietary histories, assay of social environment, and capillary resistance tests as well as routine clinical examination and periodic follow-up. Enquiry into the dietary habits indicates that the majority of the children lie on the borderline of inadequate nutrition. Many were severely deficient in vitamin C intake particularly during the winter months. In many instances the economic status precluded adequate food purchases; in other cases racial habits or individual idiosyncrasies led to a very low consumption of vitamin C-containing foods. Capillary resistance tests (an index of latent scurvy)

revealed in general low levels, particularly in cases with clinical evidence of recent rheumatic activity. Many cases showed edematous puffy gums. After an initial survey the patients were instructed to provide generous amounts of vitamin C in the diet. The usual recommendation was to prescribe a definite daily dietary supplement of orange juice (eight to sixteen ounces). Where the individuals were unable to provide this, efforts were made to secure aid from various social agencies. In most cases the period of follow-up has not been long enough to be conclusive. The group, however, has done surprisingly well from the standpoint of weight gain, general clinical improvement and absence of recurrence. The levels of capillary strength have risen. Many have passed through acute upper respiratory infections without reactivation of the rheumatic process. One recurrence occurred in a patient whom we knew had not been able to coöperate. When placed in a convalescent home where a very generous intake of vitamin C was given, the child responded remarkably with a gain of 21 pounds in eight weeks. We are cognizant of the difficulties of this method of study and particularly of the necessity of a long period of observation. Within this limit, however, we feel that the study has been very encouraging.

Summary

The experimental basis for the concept that rheumatic fever may be the result of the combined action of vitamin C deficiency and infection is reviewed. Further experimental studies are reported which confirm the original observations that this deficiency with superimposed infection produces in the guinea pig a disease state with many pathologic similarities to rheumatic fever. Comparable lesions develop in the heart valves, heart muscle and joints. The occasional occurrence of subcutaneous nodules remarkably like those of rheumatic fever would appear to complete the pathologic similarity.

Evidence is presented that the factor of infection is not specific. Essentially similar lesions develop when different organisms are used as the infecting agents. The same infections do not cause rheumatic type lesions in animals receiving adequate amounts of vitamin C.

It is suggested that vitamin C deficiency may afford the basis for the hemorrhagic manifestations frequently observed in rheumatic fever.

The epidemiological peculiarities of rheumatic fever, notably its social, geographic, and seasonal incidence, might be explained on the operation of a scorbutic factor in the disease.

Evidence indicating not only the existence, but the probably frequent occurrence of latent scurvy is reviewed. The relatively high vitamin C requirements of children, the limited capacity to store the vitamin and the possible influence of infection or fatigue in depleting this organic reserve is discussed.

Clinical studies in progress are cited that have afforded encouraging data.

Conclusions

On the basis of further experimental studies and clinical and epidemiological data, the thesis is reaffirmed that rheumatic fever may result from the combined influence of vitamin C deficiency and infection.

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NON-TRAUMATIC CHYLOTHORAX AND CHYLOPERICARDIUM; REVIEW AND REPORT OF A CASE DUE TO CARCINOMATOUS THROMBOANGIITIS OBLITERANS OF THE THORACIC DUCT AND UPPER GREAT VEINS *

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CHYLOTHORAX is a rare condition and chylopericardium still more so. Traumatic chylothorax due to rupture or section of the thoracic duct is apparently even more rare than the non-traumatic form, at least in so far as may be judged from the literature. Mouchet (1933) studied 43 cases of traumatic chylothorax reported in the literature. Perhaps twice this number of cases of the non-traumatic form have been reported.

MORBID ANATOMY

Although the exact cause of the chylothorax in many of the non-traumatic cases has not been determined, and though careful studies of the thoracic duct and veins in such cases are rare, yet review of the literature of this condition reveals that certain common causes have been demonstrated. The commonest cause seems to be compression or invasion and occlusion of the thoracic duct by a metastatic malignant tumor, sometimes with, but usually without thrombotic occlusion of the great veins of the upper part of the body. Bargebuhr (1894) reported a case due to carcinomatous invasion and occlusion of the thoracic duct secondary to carcinoma of the stomach and quoted the cases of Morton (1691), Hoffman (1700), Bass (1723), Chelchowski (1890), Zawadski (1891), Reichenbach (2 cases, 1891), Leidhecker (1893) and two additional cases of his own, all associated with neoplasms of the abdomen or thorax. In some of the cases chylous ascites also existed. The chylothorax was thought to be due to occlusion of the thoracic duct by compression by a mass or to actual neoplastic infiltration and occlusion of the duct. Carcinoma was the lesion in some of the cases, malignant lymphoma in others. Rotmann (1896) recorded three other cases from the literature due to carcinomatous involvement of the thoracic duct. Shaw (1899) reported a case of Hodgkin's disease in which the thoracic duct, which was double, became two cordlike structures buried in glands. Dock's case, studied at necropsy by Warthin (1907), was one of lymphosarcoma in which the thoracic duct had been converted into a solid cord by neoplastic invasion. In the cases of Fellner (1907) and Fürth (1927) the duct was buried in a mediastinal lymphosarcomatous mass. The cases of Sargente, Decastello and Ruddell were ap-

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parently similar cases of Hodgkin's disease. Other cases due to carcinomatous occlusion, as ascertained by necropsy, were those of Virchow, Schramm, Weigert, Cooper, Senator, Enzmann, Leschtschinski, Löffler, Hendricks, Gandin, Lyter and Fehr. The case of the last author (1930) was particularly well studied. There was carcinoma of the stomach with widespread metastases. Chylothorax was moderate but chylous ascites great. The inferior vena cava was thrombosed. The thoracic duct was buried in dense carcinomatous tissue. The coats of its wall were essentially intact, however, except for minute cancer nests in small lymph spaces in the adventitia, but its lumen was completely closed in the greater part of its course by dense connective tissue.

Perhaps the second most common cause of non-traumatic chylothorax is tuberculosis, but the mechanism here is not so obvious in some cases. Cases of this probable origin have been reported by Milton, Strauss, Bachmann, Boyer, Whitla, Morton, Hoppe-Seyler, Fowler and Godlee, Gullbring and Brandt. The case of the last named author (1917) was one with bilateral chylothorax and some chylous ascites. There was widespread miliary tuberculosis. Sections of the thoracic duct showed fibrous obliteration of the cervical portion, below which the lumen of the enlarged thoracic portion was filled with caseous masses and granulation tissue. In the wall of the duct were epithelioid cells and Langhans giant cells.

There remains a group of cases with miscellaneous causes of the chylothorax. In Rotmann's case 17 (1896) there was lymphangiectasis extending up through the abdominal lymphatics to those of the thorax. In Omerod-Wilk's case (1868) the left subclavian vein and its branches were occluded; there was also ascites. The cases of Opolzer, Renvers and Martin were quite similar in that some of the upper great veins were occluded by thrombi. Quincke (1875) reported a case in which there was inflammatory thickening of the mesentery with closure of the lymphatic vessels, resulting in both chylothorax and chylous ascites. Gandin's first case (1913) was a case of polyserositis, and his second case was one of cirrhosis of the liver, in both of which there was more chylous ascites than chylothorax. Oberndorfer (1925) reported a case of atherosclerosis of the duct, in which the lower two-thirds of the duct was filled with a blood thrombus; there was also cirrhosis of the liver and both chylothorax and chylous ascites. Engstad (1926) thought the chylothorax in his case of a large aneurysm of the aorta was due to specific ulceration of the thoracic duct. A necropsy was performed on the five-day old infant of Hilgenberg's (1929), but no cause for the chylothorax could be found. In Fehr's second case (1930), in which there was aortic regurgitation, the thoracic duct was surrounded by connective tissue, the lumen was closed and the wall was thickened with dense connective tissue. Steiner (1932) reported a case of pulmonary fibrosis in which the pleurae were 1 to 2 cm. thick, but the thoracic duct was apparently normal. In Heppner's case of bilateral chylothorax and chylous

ascites the cause was probably traumatic rupture of the thoracic duct 2.5 cm. above the diaphragm, although the reason for the rupture was not apparent.

Although this list of cases would seem to indicate that such occlusions of the thoracic duct necessarily lead to chylothorax, with or without chylous ascites, such is not the case. In the first place, there may be chylous ascites without chylothorax, and in the second place there may be neither. The former is demonstrated by the case of Monaldi (1933), in which there was gastric carcinoma with much secondary involvement of the thoracic duct but only chylous ascites. The latter is demonstrated by the cases of Andral, Rust and Otto, quoted by Boegehold (1883), of Creyx and Gauvenet (1912) and of Benda (1926), in all of which there was undoubted occlusion of the thoracic duct by malignant tissue but no accumulation of chylous fluid. Winkler and Schwedenberg, in a study of 24 reported cases of carcinomatous closure of the thoracic duct, found chylous ascites in only three. Also, 12 cases have been reported of non-tuberculous suppurative inflammation of the thoracic duct (Pappenheimer, Kryloff, Minassiantz), with occlusion thereof by a purulent exudate, but without the accumulation of chylous fluid in any of the serous cavities. In the cases of Otto and of Ameuille and Perreau the thoracic duct was extensively involved by a tuberculous process similar to that in the case of Brandt, and yet there was no transudation of chyle. McFarland (1893) reported a case of chronic congestive heart failure with almost complete occlusion of the mouth of the thoracic duct by an inflammatory thrombus and thrombosis of the subclavian and jugular veins with beginning organization; there was no chylothorax. Bigger (1907) described a chylous cyst and Wurm (1927) a fibroma of the receptaculum chyli, neither of which caused chylous ascites.

Lammers believes that no new collaterals are formed when the thoracic duct is obstructed but that the chyle and lymph may go through normal collaterals to the veins, especially when there is not much stasis but only a change in the wall of the duct. Pressure in the duct is normally low, but when it is greatly increased lymphangiectasis may develop in the tributary lymphatics and small lymph vessels may rupture or lymph and chyle may transude. This condition is especially apt to occur when there is thrombosis of the great veins into which the lymph flows as well as occlusion of the thoracic duct itself.

Fehr has advanced the theory that gradual closure of the duct does not lead to the accumulation of chylous fluid unless the collaterals are also occluded. It is the latter he believes responsible for rupture or oozing from many small lymph vessels. That this theory is probably true was shown in 1922 by Lee in his experiments with cats, in which he used an intra-thoracic method for complete ligation of the thoracic duct, the only method so far developed that is apparently faultless. He showed that the integrity of the duct is not essential to the life of the animal and that accumulation of chylous fluid in the serous cavities rarely if ever results from occlusion of the duct alone. In some of his cases in which the ligation was absolute,

collateral lymph circulation was established to the right thoracic duct, while in other cases lymphaticovenous connections were found to exist between the thoracic duct and the azygos vein.

Stuart summarizes well the variations in the communication between tributaries of the thoracic duct and the venous system, indicating how normal collaterals may carry the chyle and lymph to the veins when the duct is obstructed: "The typical description of the thoracic duct as a single channel throughout its course may almost be regarded as a description of an abnormality, so frequently is it found to branch and subdivide. In its thoracic portion it is very common to find it breaking up into two divisions, which reunite higher, enclosing a space technically named an 'insula,' which is often crossed by a plexus of communicating channels. Rarely the duct may remain double throughout. These insulae in the thorax are surgically unimportant, but the same tendency may manifest itself at the termination of the duct in the neck, so that it either opens in a delta-like manner by several fine channels in its usual situation, or actually terminates in two or more important branches, which enter different veins. Teichmann regards this multiple insertion as normal. Not uncommonly one branch enters the left subclavian vein, while another joins the left internal jugular; sometimes they enter the right and the left subclavian respectively. Verneuil records a sixfold division, two branches ending in the left subclavian, two in the external jugular and two in the vertebral. Verneuil quotes the results of Boullard's researches, namely, that in 24 cases the opening of the duct was 18 times single, thrice double, twice triple, and once sixfold. Wendel, in 17 cases, once found the opening triple, thrice double, while in four instances there were several branches.

"A second abnormality in the relation of the thoracic duct to the great veins is that it may, while terminating in a single channel, open in some more or less unusual situation. Thus it may enter the left subclavian vein, the left internal jugular, the right internal jugular, or the right subclavian; in the last case the right lymphatic duct generally ends in the veins of the left side of the neck. Wutzer reports a case of its termination in the vena azygos major at the sixth dorsal vertebra, and Henle, who had doubts with respect to several similar recorded instances, regards Wutzer's case as undeniable.

"A third and extremely important point is the frequent existence of communications between the thoracic duct and the various veins during the upward course of the former through the abdomen and thorax. This we might expect from a study of comparative anatomy, for in birds lymphatics of the lower extremities open into the veins of the thigh and pelvis; in amphibians and fish analogous lymphatics have a corresponding ending; and in the pig there are said to be regular communications between the thoracic duct and the azygos vein. In man Wendel regards a branch between the duct and the azygos major as almost a normal condition. Connections with the iliac and lumbar veins, the inferior vena cava, and the left renal vein

through the lumbar lymphatics have also been observed. In some of the older cases it is possible that there had been pressure on the duct above, and that these connecting vessels had originally possessed only a tiny lumen. A good account of the variations in the thoracic duct in this and other respects is contained in the volume by Poirier, Cuneo, and Delamere."

Symptomatology

Besides the cases already mentioned, in many of which necropsies were performed, a number of other cases of chylothorax have been described from the clinical standpoint only (Neuenkirchen, Whyte, Syers, Veiel sen, Campbell, Lotheissen, Erb, Kamienski, Rosin, Strasser, Sherman, Jennings and Rich, Lammers, Hyde, Sale, Günder, de Lange, Chevrel, Lewin, Pisek, Hüssey, Williamson, Gralka, Wilhelm, Remé, Stewart and Linner, Felts, Foley).* In some of these clinical cases there was evidence of the probable underlying morbid anatomy causing the chylothorax. These were mainly cases of tuberculosis, Hodgkin's disease and lymphosarcoma. The ages of the patients varied from early infancy to moderately advanced old age. Males predominated. The symptoms and signs were naturally dependent upon the underlying cause and the amount of chylous accumulation. The first symptoms were sometimes those of massive pleural effusions. The amount of accumulated milky fluid was sometimes small, sometimes great. Occasionally both pleural cavities contained chylous fluid. Chylous ascites occurred in perhaps half of the cases and chylopericardium in three (including that here reported). The thorax was aspirated a variable number of times. In Felts' case the thorax was tapped 40 times and the abdomen 13 over a period of months, a total of 235 pounds of fluid being obtained with a loss in body weight of only eight pounds. Hyde tapped his patient 21 times, withdrawing 48,139 c.c. of chylous fluid. Milton withdrew 15 pints of chyle (23 pounds) from the pleural cavity at one sitting over a period of six hours, the patient recovering without further aspiration. Lammers' patient coughed up about one-quarter of a liter of chylous fluid on two occasions, and Campbell's patient 25 c.c. Lyter's patient vomited milky fluid. Pisek gave his infant patient Sudan III and found the aspirated chylous fluid to have become pink. Stewart and Linner injected Congo red intraperitoneally and obtained pink chylous fluid from the chest.

Emaciation may result from loss of chyle, containing the fat absorbed from the lacteals. The degree of emaciation depends upon the appetite of the patient, the underlying morbid anatomy, the amount of chyle aspirated, the rapidity of its re-accumulation and the ratio between the amount of chyle entering the veins through collaterals and the amount transuding into the serous cavities. The degree of emaciation may be greater with traumatic rupture of the thoracic duct as long as the defect remains open because of the greater amount of chyle escaping directly into the serous cavities.

* A very few other cases of chylothorax have been reported in the literature, but they were either not available or could not be translated.

Felts' case, mentioned above, illustrates, however, the possibility of the benignity of the loss of chyle in large amounts under favorable conditions.

In a few cases in which chylous fluid has been aspirated from serous cavities during life it has been found later at necropsy to have disappeared. This disappearance may have been due to the opening up of normal collaterals.

Character of the Fluid

There has been considerable discussion in the literature regarding the characteristics of the chylous fluid. The differentiation between chylous and chyliform or pseudo-chylous fluid has frequently been made, with what appears to be a lack of clear distinction. Chyliform fluid has been thought to be due to fatty degeneration of the leukocytes of a purulent exudate and if it exists is apparently even more rare than the abnormal accumulation of chyle itself. Even a third form of fluid has been described as lactescent, non-chylous fluid, a milky effusion in which there were no fat globules but a "glyco-proteid" (Lion). The probability is that chylous and chyliform fluids are essentially the same and are both due to transudation of chyle and lymph. There appears to be considerable difference in the chemical and physical properties of the fluid in different cases, and this may account for the distinction. The size of the fat droplets; the presence and amount of various lipids, especially lecithoprotein; the varying amounts of chyle, lymph and inflammatory and neoplastic exudates; and the character and quantity of food ingested are all factors. There is no parallelism between the degree of turbidity, milkiness or opalescence and the amount of fat. In general, the smaller the size of the fat droplets, the more lactescent the fluid.

Most knowledge of the composition of chyle has been obtained from the study of a mixture of chyle and lymph obtained through a cannula in the thoracic duct of dogs. The chyle of a mixed diet is a white opaque fluid, occasionally tinged red or yellow from an admixture with red blood cells. In herbivora it may be greenish from the presence of chlorophyll. It is alkaline due to the presence of carbonates and phosphates of sodium. The specific gravity ranges between 1.018 and 1.025. It has a salty taste. It possesses an odor due to volatile fatty acids. It coagulates on standing, and a top creamy layer forms. Shaking with ether after alkali is added causes the fluid to become clear. Microscopically, many fine fat granules are seen which have a peculiar Brownian movement. There may be some white blood cells, mainly lymphocytes.

The chemical analyses in man (Munk) of chyle and lymph are as follows:

	Chyle	Lymph
Water	92.2 per cent	95.2 per cent
Solid	7.8 " "	4.8 " "
Fibrin	0.1 " "	1.0 " "
Proteids	3.2 " "	3.5 " "
Fats, lecithin and cholesterin	3.3 " "	traces
Extractives	0.4 " "	0.4 " "
Salt	0.8 " "	0.8 " "

Exceptionally chyle contains more sugar than lymph. Chyle contains more fat than lymph and less protein than blood plasma. The amount of urea is greater than in blood. The soaps in chyle are less than 0.2 per cent, the fat being almost all neutral fat. The fat granules are less than one micron in diameter. For discussions on the characteristics of chylous and so-called chyliform fluids one may refer to the papers of Shaw, Sherman, Lammers, Gandin, Lewin and Fürth.

The normal amount of chyle flowing through the duct (Noel Patton) is 130 to 195 c.c. per hour, being greater after a meal.

Prognosis

The prognosis depends largely upon the underlying cause of the chylothorax. In many cases this is a fatal neoplastic disease. A number of recoveries have been reported, however, after one or more aspirations of the fluid. The condition may last for months or years, with or without recovery. Traumatic chylothorax is more favorable, since a small opening in the wall of the thoracic duct may become closed by a thrombus or the duct itself may become thrombosed. Also, if the duct is ligated below the defect the collaterals may carry the chyle and lymph to the veins.

Treatment

The treatment is mainly that of the underlying disease. The chyle should be aspirated if it causes much respiratory embarrassment; otherwise, it probably should not be withdrawn, since it is apt to re-accumulate rapidly. The diet probably should consist largely of carbohydrates and proteins, and fluid should be taken only between meals in small amounts at a time.

Case Report

A white woman, aged 47 years, was admitted to the Gallinger Municipal Hospital on January 19, 1934, complaining of difficulty in breathing and swelling of the face and neck. She had been well prior to five weeks before admission, except for scarlet fever in childhood and pneumonia about 20 years before. She had two children. The family history was irrelevant. Five weeks before admission she had been handled roughly by her nephew who playfully attempted to demonstrate a wrestling bout he had just witnessed. Her neck had been bent painfully. The following day she first noticed swelling of the neck and face, which varied in amount from time to time. Four days before admission she began to have difficulty in breathing and noticed distention of the veins over the chest and in the neck.

On admission the patient appeared to be in extremis. She was very cyanotic and extremely dyspneic. Artificial respiration caused great diminution in the degree of cyanosis and made her comfortable. She spent the first night in a Drinker respirator. On examination the following day she was described as being a moderately obese woman, sitting upright and breathing rapidly and shallowly. The upper half of the body was definitely cyanotic. The face was slightly swollen, and the neck was so swollen that all landmarks were obliterated. There was edema of the chest wall down to the costal margin and distention of the superficial veins. From the fourth rib downward posteriorly and the third rib downward anteriorly on the

right side there were diminished tactile fremitus and dullness. The breath sounds in this region were distant with a bronchial quality. There were numerous inspiratory and expiratory râles. The spoken and whispered voice sounds were transmitted very distinctly. The physical signs on the left side were normal but exaggerated, with musical râles at the end of inspiration. The outline of the heart was not definite. The rate was 100 per minute with regular rhythm. The blood pressure in the right arm was 115 systolic but the diastolic could not be estimated; it was 140 systolic and 110 diastolic in the left arm. The abdomen was negative. A pelvic examination was not made because of the patient's serious condition. There was moderate edema of the upper extremities, none of the lower. The temperature was 100° F. The respiratory rate was 30 per minute. Aspiration of the right pleural space produced 1500 c.c. of a lactescent fluid, which on microscopic examination revealed myriads of fine globules possessing a Brownian movement. The chemical composition of this fluid was as follows:

Fat	2.04 per cent
Serum globulin	0.71 " "
Serum albumin	2.07 " "
Non-protein nitrogen	32 mg. per 100 c.c.
Urea nitrogen	14 mg. " " "
Chlorides	540 mg. " " "
Cholesterol	80 mg. " " "

Urinalysis was negative. The hemoglobin was 80 per cent, the erythrocytes numbered 4,870,000 and the white blood cells 8,600 per cubic millimeter of blood, with 52 per cent polymorphonuclear neutrophiles, 1 per cent eosinophiles, 24 per cent band cells, 3 per cent young cells, 14 per cent lymphocytes and 6 per cent large mononuclears. The blood urea nitrogen was 13 mg. per 100 c.c., the blood sugar 95 mg., the blood cholesterol 113 mg., the serum albumin 3.56 per cent and the serum globulin 0.97 per cent.

Fluorscopic examinations of the chest showed varying amounts of fluid in both sides and an abnormal shadow in the anterior superior mediastinum.

The patient was in the hospital 10 days before death. Her chest was aspirated three more times, once on the left side (750 c.c.) and twice on the right side (1300 c.c. each). For a while she seemed to improve greatly, the dyspnea, edema and cyanosis all diminishing. After three days the temperature became normal and remained so. The pulse rate varied considerably from 68 to 128. There was apparently little loss of weight. Death occurred on January 30 during a sudden attack of severe orthopnea, in which there was very little cyanosis.

Necropsy. Necropsy was performed under difficulties but quite thoroughly. The neck was markedly swollen, and there was pitting edema of the upper arms and of the thoracic wall. While cutting through the subcutaneous tissues and muscles of the chest wall, all of the veins were observed to be thrombosed. Upon opening the thoracic cavity a large amount of milk-like fluid poured out of both pleural cavities, there being approximately three liters in the right and two in the left. The pericardial sac was distended with about 250 c.c. of the same fluid, and the transverse diameter of the sac was about 13 cm. When the heart was removed the superior vena cava was seen to be filled with a crumbly, light gray thrombus, and its wall was thickened. As the vena cava was dissected upward, it was noted that both innominate veins were completely occluded by what appeared to be an organized thrombus. This condition existed up to a point above which the subclavian veins should have joined the jugular veins. The subclavian vein on each side was a mere fibrous cord and difficult to find. The jugular veins were filled with ordinary, non-organized thrombi, that on the left being distended to a diameter of 2 cm. for a distance of about 4 cm., that on the right having about half this diameter. Some lymph nodes about 1.5 cm.

long were noted near the superior vena cava, and on sectioning were found to be firm and white, resembling carcinomatous lymph nodes. The lymphatic vessels in the thorax were not grossly visible. The thoracic duct was dissected out from the cisterna chyli to its point of entrance into the jugular vein. It was apparently normal except for the final centimeter, where it was dilated to almost 3 mm. and felt firm. A lymph node about 1 cm. long was found near the mouth of the thoracic duct and appeared grossly carcinomatous. A right lymphatic duct could not be found. The inferior vena cava and the veins draining into it were not thrombosed. Grossly the heart was in every way normal. The lower lobes of the lungs were moderately collapsed, the upper lobes containing air and the left upper lobe being somewhat emphysematous. There were a few small adhesions at the apices and bases. The abdominal cavity did not contain fluid. The liver was moderately enlarged, extending downward about 5 cm. below the right costal margin and about 10 cm. below the xiphoid process. There were a few filmy fibrous adhesions over the upper surface of the liver. Similar adhesions joined the under surface of the right lobe of the liver and the great omentum. There were also a few adhesions over the posterior surface of the spleen, which was grossly normal. The abdominal viscera appeared normal, except the ovaries, which were carcinomatous. The right measured about 11 by 9 cm. and consisted of a capsule tensely distended with a clear watery fluid which coagulated after it was placed in formalin. On the external surface there were papillomatous excrescences. The left ovary resembled it but measured only 5 by 3 cm. There was no evidence of gross metastases except to the lymph nodes previously mentioned in the superior mediastinum.

Microscopic Study. Sections through the superior vena cava showed that vessel to be filled with a thrombus. Organization was extending into this from the wall of the vein and had reached about one-fifth of the distance to the center of the thrombus. No tumor cells were seen in the wall of the vessel or in the thrombus. One lymph node adjacent to the vein appeared to be normal except for the usual amount of anthracosis. Another small lymph node nearby showed some small groups of tumor cells in its peripheral portion. In the connective tissue adjacent to the vena cava some of the small veins and an occasional arteriole were surrounded by small lymphocytes. The vein wall was greatly altered.

Sections through the middle portion of the right innominate vein showed that vessel to be completely occluded by an organizing thrombus, the organization having extended in toward the middle of the lumen about half way. The greatly altered wall of the vein contained numerous small lymphocytes. A few endothelial-lined spaces in the peripheral portion of the thrombus contained tumor cells. It was impossible to trace the vein wall completely because of fusion with the surrounding tissues by a marked fibroblastic reaction (figure 1).

Sections through the right innominate vein at its point of origin showed it to be completely occluded by a completely organized thrombus containing many endothelial-lined spaces, many containing blood, others containing only nests of tumor cells. About those containing tumor cells were numerous small lymphocytes. Some of the small vascular channels in the thrombus were thrombosed. At some distance outside of the vein there was a group of large, rounded spaces lined by and containing in their lumen tumor cells and a network of fibrin. About these spaces was dense fibrous connective tissue, and the small vascular channels therein were densely surrounded by small lymphocytes.

Sections through the middle portion of the left innominate vein showed essentially the same picture as those through the same portion of the right, but no tumor cells were seen. More of the small vascular channels in the organizing thrombus contained thrombi.

Sections made at short intervals through the first 1.5 cm. of the left innominate vein just below the junction of the jugular and subclavian veins showed that there

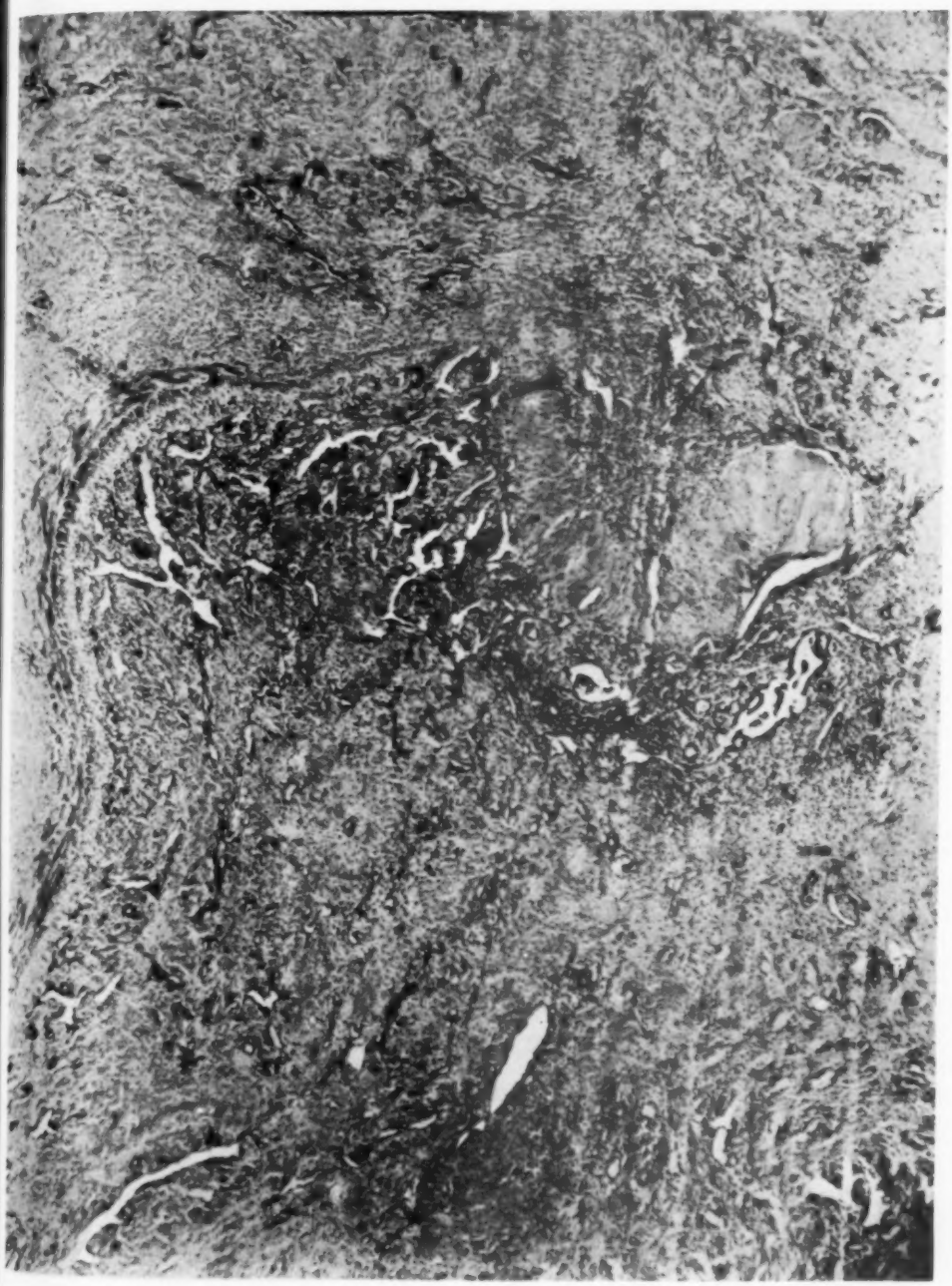

FIG. 1. Partial cross section of the right innominate vein and surrounding tissue, showing the organized thrombus within the vein, nests of neoplastic cells just within its wall and the fibroblastic reaction in the adjacent connective tissue above. × 60.

was complete occlusion by a thrombus which was completely organized by the oldest-appearing connective tissue just at the origin of the vein. In the lower sections of this part of the vein the central portion in the thrombus had not become organized. There were more small lymphocytes in the organized thrombus of the left innominate vein than in the thrombus of the right innominate vein at the same point. There were, however, fewer spaces containing tumor cells. At this point there were also fewer nests or channels containing tumor cells in the connective tissue surrounding the vein. What was apparently the subclavian vein was seen to be completely organized into a fibrous cord.

Just above this point, i.e., in the lowest portion of the left jugular vein, the same picture was seen, with the central portion of the thrombus unorganized. There were a very few spaces in the wall of the vein, just within its muscular coat, lined with tumor cells.

Sections through the dilated portion of the left jugular vein showed this to contain an unorganized thrombus. The wall of the vein was greatly altered, with increased vascularity and a rim of dense lymphocytic infiltration. A small adjacent lymph node did not contain tumor cells.

Sections at short intervals through the bulbous terminal portion of the thoracic duct showed that vessel to be double at that point and presenting the picture seen in advanced cases of thromboangiitis obliterans. There remained none of the thrombus which had undoubtedly originally existed in the lumina. This had become completely organized and canalized by irregular channels of various sizes and shapes lined by endothelium. In each duct there was an eccentric, slit-like channel which apparently represented the main new channel of the duct. The organized thrombus of one of the ducts was particularly well vascularized. At isolated and infrequent points in the region where the intima of the ducts probably once existed there were spaces containing tumor cells (figures 2 and 3). Sections through the upper, middle and lower thirds of the main duct below its bulbous terminal portion showed the lumen to be open and the wall relatively little affected.

The lymph node in the immediate vicinity of the end of the thoracic duct contained many nests of tumor cells. The adenomatous nature of the neoplasms was well demonstrated in many of these nests. Some of the nests were endothelial-lined structures containing masses of tumor cells, others were spaces lined by tumor cells and presenting an adenomatous formation. There were also isolated tumor cells in many of the pulp sinusoids, indicating retrograde involvement of the node through its duct. The tumor cells were moderately large epithelial cells with round nuclei of about the same size. Many of the cells were " signet-ring " cells, usually larger than the others and containing a large vacuole-like portion with the nucleus more or less flattened and crescentic at the periphery. There was relatively little cytoplasm. The cells were well differentiated and strongly resembled those of the ovarian tumors. Many psammomatous bodies were seen in the cell nests. These were rounded masses having a black peripheral zone with a refractive central portion. They presented the appearance of whorls. Sections made through the tissue adjacent to this lymph node in the supposed region of its duct showed a structure which may have been the duct. It contained no tumor cells in its lumen.

Sections through the walls of the ovaries showed typical adenocarcinoma of papillary structure. There was one layer of columnar epithelial cells with elongated nuclei. Most of the groundwork was a delicate reticulum of young fibrous connective tissue. In some of the fimbriae this reticulum was a homogeneous, hyaline-like material containing a large number of extravasated erythrocytes.

Sections of the other organs revealed nothing of importance.

Interpretation of Evidence. The most logical interpretation of the series of events in this case is as follows. A few of the columnar epithelial cells of the poly-

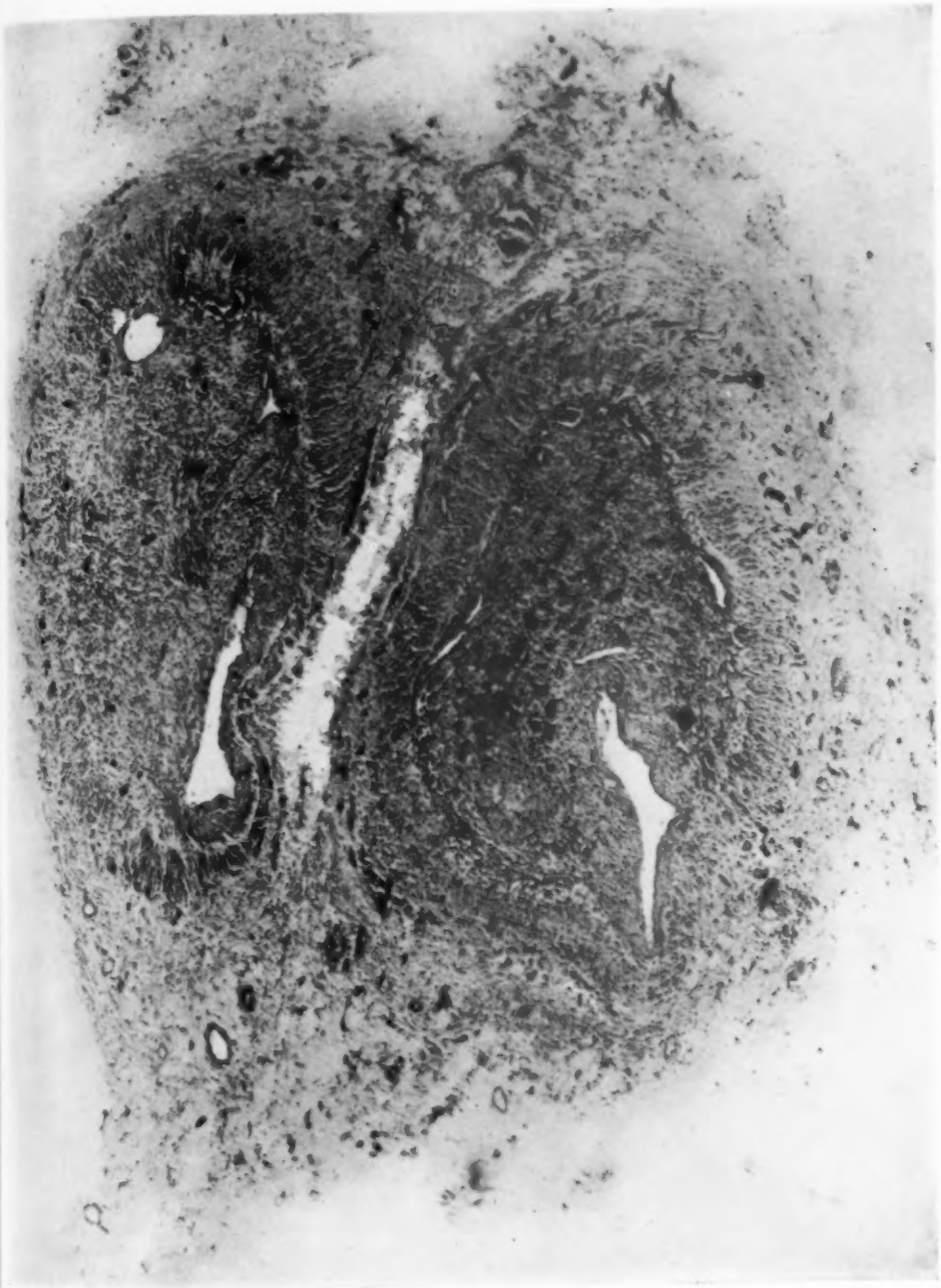

FIG. 2. Cross section of the double terminal portion of the thoracic duct, showing the result of organization and canalization of thrombi in the lumina of the two arms. Small nests of carcinoma cells may be seen in the upper part of each vessel, in the probable region of the original intima. The organized thrombus of the vessel on the right is quite vascular. × 60.

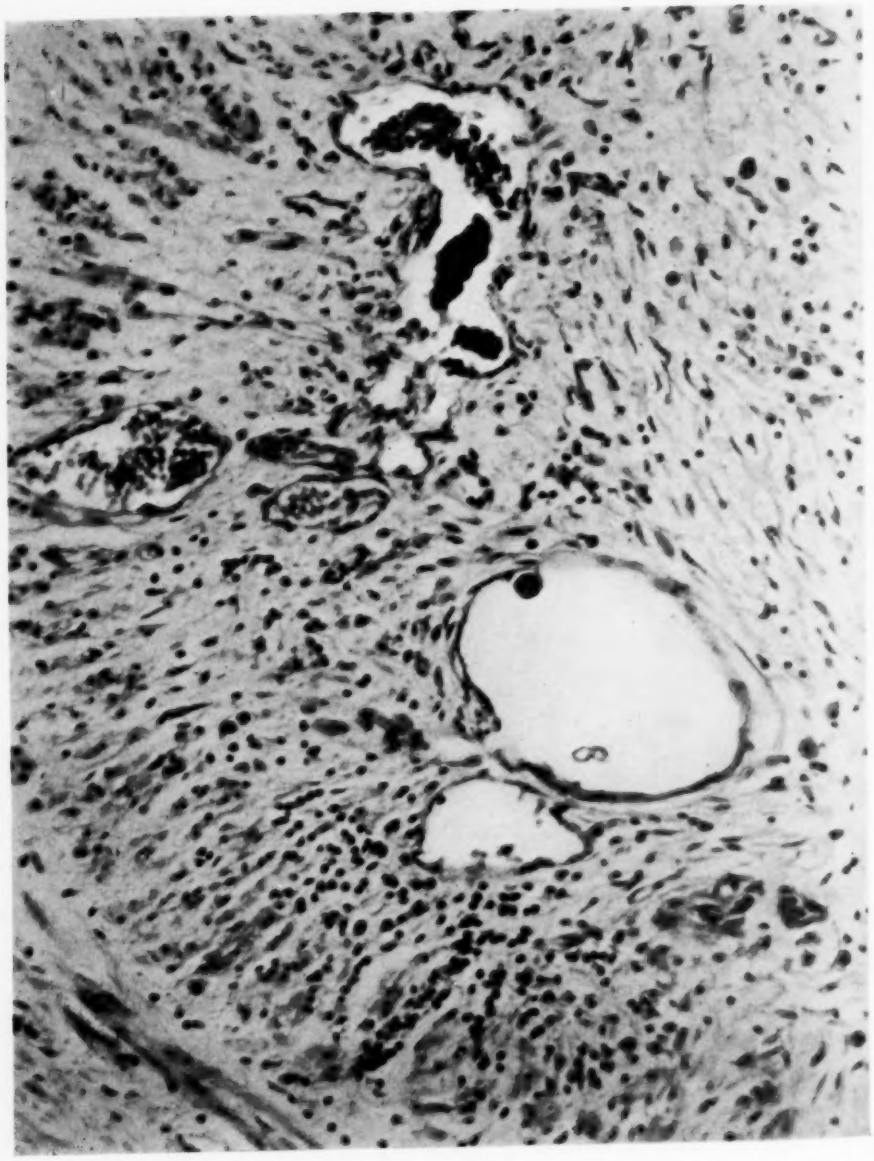

FIG. 3. Enlargement of the upper portion of the wall of the vessel on the left shown in figure 2. An endothelial-lined space containing carcinoma cells may be seen, to the left of which is a similar round space containing a pearl-like body on its wall. × 375.

poid carcinomata of the ovaries broke loose from the tumor or tumors into the peritoneal cavity. Here they were taken up by the lymphatics and entered the thoracic duct. They became lodged in the upper end of the duct, acted as an irritant to the intima and caused the formation of a thrombus which became organized and recanalized. Owing to the stasis in the duct produced by this obstruction, some of the neoplastic cells were forced into the ducts of the lymph nodes in the superior mediastinum and began to proliferate in the nodes. Some of the cells lodged also in the walls of the upper great veins. There the same process was initiated on the intima of the veins as occurred in the thoracic duct. The injury to the neck probably speeded up the process of thrombosis and organization of these veins, causing damage to them in their indurated state.

Summary and Conclusions

1. Non-traumatic chylothorax is rare, perhaps less than 100 cases having been reported in the literature. Chylopericardium is very rare, only three cases, including the one here described, having been observed.

2. The commonest cause of non-traumatic chylothorax is apparently malignant neoplastic compression or occlusion of the thoracic duct, probably with closure of its collaterals. The second most common cause seems to be pulmonary, pleural, and glandular tuberculosis associated with occlusion of the thoracic duct and its collaterals. There is also a miscellaneous group of causes, chief among which is thrombotic occlusion of the great veins of the superior mediastinum.

3. Many cases of obstruction of the thoracic duct are not associated with the accumulation of chylous fluid because of the normal collaterals which empty into veins.

4. The physical and chemical composition of the chylous fluid probably depends largely upon the relative amounts therein of chyle, lymph, inflammatory and neoplastic exudates and lipids of varying chemical constitution and physical state. So-called chyliform fluid due to fatty degeneration of leukocytes in an inflammatory exudate probably does not exist.

5. Prognosis depends mainly upon the cause of the chylothorax, and treatment is largely symptomatic and supportive.

6. A case of bilateral chylothorax and chylopericardium is reported, with necropsy findings and detailed study of the thoracic duct and the upper great veins. The patient had bilateral cystadenocarcinoma of the ovaries with metastases to the upper end of the thoracic duct, the walls of the upper great veins and the lymph nodes of the superior mediastinum. The mouth of the thoracic duct and the veins had become thrombosed and organized. The duct had been recanalized.

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ALTERATIONS IN HEPATIC FUNCTION PRODUCED BY EXPERIMENTAL HEPATIC LESIONS *

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In the course of our studies of hepatic function in the experimental animal many of our observations have appeared to be of clinical interest. While direct transposition of experimental data to clinical practice is unwise, anyone would agree that differences attributable to species are minor points compared to the major problems of hepatic disease, and that such differences will find simple explanation with complete understanding of the physiology and the pathology of the liver. It will not be necessary to call attention to the many similarities that appear in animals with experimentally produced lesions of the liver and in human beings with disease affecting that organ. The conclusions we have reached were based entirely on experimental observations, but we feel safe in saying that, under similar circumstances, they are equally true for man.

Before discussing the functions of the liver which are altered by pathologic changes in that organ, we would sharply separate two types of hepatic lesions. These two types are not the acute and chronic, although this classification would in many cases effect the same separation. Our first type is based on changes produced by injury to the cells of the liver so that their functional capacity is altered, and the second type is produced by a reduction in the number of functioning hepatic cells. In the first type many of the functions of the liver may remain, and the symptoms noted may be due partly to loss of other function and to toxemia, and to absorption of toxic material from necrotic cells in the liver. The second type is that produced by surgical removal of large amounts of hepatic tissue or by gradual removal of hepatic cells killed by toxic agents when the regenerative processes of the liver have failed. In advanced atrophic cirrhosis, some of the symptoms appear to be the result of the diminished number of cells in the liver which have been replaced by connective tissue. For the most part, however, both types of pathologic changes in the liver are present. Even in the acute hepatic necrosis produced by chloroform or carbon tetrachloride some symptoms may be attributed to the absence of hepatic function, but the chemical and metabolic changes found are not of the same magnitude as occur at death in the liverless animal.[2] The fatal outcome following administration of these hepatic poisons must be attributed to other factors, such as the formation of toxins in the liver by the necrotizing action of the toxic agent.

The rarity of death from hepatic failure, comparable to the death of animals following complete removal of the liver, is apparent from the few re-

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ports of this condition in the literature. Stadie and Van Slyke and Rabinowitch have each reported cases in which the blood and urine showed changes similar to those found after complete removal of the liver of animals. Such changes as we have reported are always found in the liverless animal, so that the absence of such changes must mean that some hepatic tissue remains functioning or that some of the substances which would ordinarily disappear are being replaced by the treatment which is being employed. After complete removal of the liver and recovery from anesthesia, the animal appears normal for two to twelve hours until symptoms of hypoglycemia appear.[9] Such symptoms are promptly dispelled by the administration of glucose, and they will not recur if sufficient glucose is given to prevent the sugar content of the blood from reaching hypoglycemic levels. If the supply of glucose is maintained, the animal will remain in apparently normal condition for many hours, usually from 24 to 56 hours. Characteristic symptoms then develop: the reflexes disappear, convulsions occur, and the animal dies. This sequence of symptoms is run in one to six hours, and we have been unable to alter this course.

Many of the chemical changes that accompany removal of the liver are very definite. There is a progressive decline in the sugar content of the blood, which cannot be reversed by methods that raise the blood sugar in normal animals, except by the administration of glucose or a few substances which in the animal organism are readily converted to glucose. Urea ceases to be formed and there is a decrease in the urea content of the blood equivalent to the amount of urea excreted in the urine.[5] Deaminization of amino acids does not occur and there is a marked increase in the amino acid content of the blood, urine, and tissues.[7] Destruction of uric acid ceases and there is an increase in the uric acid content of the blood and urine.[6] Jaundice occurs, with retention of bilirubin in the blood. The reaction of the retained bilirubin is " indirect " to the Van den Bergh reagent.[3] If jaundice is produced by occlusion of the common bile duct or by extensive degenerative changes in the liver, the reaction of bilirubin in the serum is " direct " to the Van den Bergh reagent. Subsequent removal of the liver under these conditions further increases the bilirubin content of the blood, but the increase is only that of " indirect " bilirubin whereas the former level of " direct " bilirubin remains unchanged or decreases due to excretion of this substance by the kidneys. Complete failure of hepatic function should therefore increase the amount of " indirect " reacting bilirubin in the blood. We have not observed this in any case of hepatic failure produced by acute or chronic toxic degeneration of the liver, so that it would appear that this function of the liver is quite persistent and can be accomplished by small amounts of functioning hepatic cells.

Most of these functions of the liver may be performed completely by only a small amount of that organ.[8] McMaster and Rous found that the hepatic bile ducts from as much as 80 per cent of the liver could be ligated without the retention of bilirubin in the blood. We have been able to remove large

portions of the liver of animals, so that less than 20 per cent remained, without permanently interfering with the excretion of bilirubin. Under these circumstances there is usually some retention of bilirubin for the first few days after operation, but this is a result of edema and other changes in the liver caused in turn by the surgical manipulation and factors connected with the operation. After recovery from these acute effects, bilirubinemia disappears and many other functions of the liver appear normal. The regulation of blood sugar, the formation of urea, deaminization, the destruction of uric acid, the utilization of glucose, levulose, and galactose, and the excretion of bromsulphalein, rose bengal, and so forth, are not materially altered from what is found in the normal animal. Regeneration of hepatic tissue occurs rapidly following partial removal of the liver of normal animals,[10] but normal function returns before hepatic tissue has been completely restored, and function returns similarly in animals in which restoration has been prevented. Similar retention of liver function is seen in animals with experimental cirrhosis sufficient to destroy a large portion of the liver.[1] Even in extreme conditions many of the measurable functions of the liver appear to be within normal limits.

Certain other functions of the liver appear to be more easily influenced by induced pathologic changes. Smith and Whipple have demonstrated that the liver forms bile salts. In their animals which had complete biliary fistulas the daily excretion of bile salts depended somewhat on the nature of the diet, being about 100 mg. of taurocholic acid per kilogram of body weight. Fasting or feeding with sugar reduced this figure to 20 or 40 mg. Feeding liver, kidney, or beef muscle produced from 200 to 300 mg. of taurocholic acid per kilogram of body weight in 24 hours. Bile salts administered by vein or by mouth were quantitatively excreted into the bile. Mild hepatic injury, such as is produced by small amounts of chloroform or by an Eck fistula, may greatly reduce the amount of bile salts formed. In these cases the reduction in the amount of bile salts formed is coincident with the injury produced in the liver, but the same is not true following phosphorus poisoning which may produce extensive lesions in the liver with but little reduction in the excretion of bile salts.

Although glycocholates and taurocholates administered by vein or by mouth are completely excreted in the bile, they are also reabsorbed from the intestine unless the bile is withdrawn as in the animal with a biliary fistula. Continued feeding of large amounts of bile salts, however, does not produce an accumulation of these substances in the body, nor are they excreted as such in the urine or feces. The liver regulates the amount of bile salts by destroying the excess and by forming more when the supply is low if the necessary materials are provided. Following ligation of the common bile duct, bile salts appear in the urine in fairly constant amounts, somewhat less than are excreted in the bile of animals with biliary fistulas. Administration of bile salts increases the bile salt content of the urine, but a considerable portion of the bile salts is destroyed. If the liver is removed completely,

all of the bile salts administered appear in the urine within a few hours, and in the absence of the liver no evidence of the destruction of bile salts is found. The rôle of the liver in the formation of bile salts is established by the fact that, while small amounts of administered bile salts are completely recovered in the absence of the liver, no bile salts can be detected in the blood or urine following removal of the liver unless bile salts have been administered.[4] The fact that bilirubinemia and bilirubinuria develop in the absence of the liver again indicates the difference in the metabolic formation of bile pigment and bile salts.

With complete biliary obstruction, the dog excretes bile salts in the urine and bile salts are present in the blood. With continued jaundice and progressing hepatic deficiency, less bile salts are excreted. Additional injury to the liver by chloroform, carbon tetrachloride, or toluylenediamine further reduces the amount of bile salts in the urine to very small amounts, and markedly reduces the level of bile salts in the blood. Thus the presence of bile salts in the blood and urine of dogs with completely ligated bile ducts indicates the presence of a liver with otherwise good functional capacity, and the absence of bile salts from the blood indicates impaired hepatic function. This observation can frequently be confirmed by a decreased utilization of galactose, but we have had several cases in which the histologic picture in the liver corresponded much better with the bile salt findings than with the results of the galactose test.

The presence or absence of bile salts in the blood might appear as a good index in the troublesome problem of differentiating obstructive jaundice and intrahepatic jaundice of toxic origin. Certainly in the experimental animal such differentiation can be made if due regard is paid to the course of the jaundice. Jaundice produced in otherwise normal animals by the administration of hepatic toxins, such as chloroform, phosphorus, carbon tetrachloride, tetrachlorethane, or toluylenediamine, has certain features in common with obstructive jaundice in that bile salts are found in the blood and urine for a few days. As the animals recover, the bile salts disappear from the blood and urine, while the bile pigment is diminishing. Additional hepatic injury, by repeated administration of the toxic agent, also causes the bile salts to disappear from the blood and urine while bilirubinemia is increased by added injury to the liver. The level of bile salts in the blood of dogs with obstructive jaundice, while the liver is in good condition, is higher than that found in the jaundice produced by toxic agents.

The detoxicating functions of the liver also appear to be definitely influenced by the condition of that organ. We have not been very successful in measuring the detoxicating function of the liver by chemical methods, but biologic methods seem to be much more sensitive under the conditions we have studied. Satisfactory approximations may be made of the differences in detoxication by clinical observations of the effects of the toxic agent and the microscopic examination of the effects on hepatic tissue. Numerous experiments indicate that the systemic and local effect of many toxic agents

is dependent on the condition of the liver at the time of administration of the toxin. Marked changes occur in the chemical composition and microscopic appearance of the liver under normal conditions with relation to the taking of food. A short time after a meal the glycogen content and water content of the liver increase somewhat in proportion to the amount and nature of the food taken. Shortly after digestion is complete the glycogen content of the liver again decreases. By feeding unbalanced diets, greater changes may be made which have less daily variation. By feeding a diet rich in carbohydrate, the glycogen content of the liver may be increased from a normal of 2 to 5 per cent to about 15 per cent, and it may be raised to as much as 25 per cent by intravenous injection of large amounts of glucose. Such measures increase the water content of the liver and reduce the fat content. With excessive fat diets the fat content of the liver may be increased from 3 per cent to as much as 50 per cent of the weight of the liver, and at the same time the water content may be reduced from 72 per cent to 30 per cent and the glycogen content to 0.1 per cent. It is interesting to note that the liver is able to maintain its ordinary functions without impairment except in extreme conditions.

We have many times noted that the reaction to toxic agents, both from the viewpoint of systemic reaction and the injury produced in the liver, varied with the diet of the animal and the chemical composition of the liver. The survival time and general well-being of the animal after complete occlusion of the common bile duct are markedly improved by a diet rich in carbohydrate. Dogs survive from six to twelve months after ligation of the common bile duct if fed a diet rich in carbohydrate. Similar animals fed diets rich in protein seldom survive more than three months. Similarly, animals fed carbohydrate withstand repeated administration of carbon tetrachloride in amounts which prove fatal to those fed protein, and particularly to those on a fat diet. The diets we have used have all been adequate in maintaining the untreated animals indefinitely. The appearance of the lesions produced in the liver has also been correspondingly less in the animals fed carbohydrate. The difference in the systemic effect of tetrachlorethane is very marked, even with daily variation in the glycogen content of the liver, when the animals are fed a carbohydrate diet once daily. A small dose of tetrachlorethane (1 c.c.) produces marked intoxication and coma of six to eight hours' duration when administered 24 hours after the last feeding; at 18 hours the effect is noticeably less, and at 12 hours only a mild intoxication is noted. If the same dose of tetrachlorethane is given from one to six hours after feeding, no visible effect is noted. The lesions produced in the liver by this drug are also in proportion to its systemic effect.

We attempted to correlate the effects of carbon tetrachloride and tetrachlorethane on the liver with the marked changes produced in it by diets rich in fat and poor in carbohydrate, but we were not very successful. Small amounts of these toxic agents produced no effect when the liver was rich in

glycogen, but proved fatal within 24 hours if the liver was fatty at the time of administration. With smaller doses inconsistent results were obtained, some fat-fed animals were unaffected by amounts that were fatal to others, and the lesions in the liver likewise were not constant.

The reaction to ethyl alcohol is a good means of illustrating variations in susceptibility corresponding to the glycogen content of the liver as varied by dietary means. With the fat diet we have used there is not much change in the composition of the liver during the first week of its administration, but during the second week the percentage of fat begins to increase and the glycogen to decrease. By the third week the fat content has risen to around 20 per cent and by the fourth week to 40 per cent. Glycogen decreases in the second week to less than 1 per cent, and gradually declines to 0.2 or 0.3 per cent in the third and fourth weeks. We injected dilute alcohol intravenously to eliminate possible variations in the rate of intestinal absorption. When the glycogen and fat of the liver were normal, dogs momentarily become intoxicated with the injection of the equivalent of 1.5 c.c. of 95 per cent alcohol per kilogram of body weight, and definite intoxication of about 30 minutes' duration followed the injection of 2.0 c.c. Larger amounts proved fatal. Animals that were fed carbohydrate diets, so that the glycogen content of the liver was more than twice the normal value at the corresponding time following the meals, gave evidence of only momentary intoxication with 2 c.c. of alcohol per kilogram of body weight. The first week on the fat diet did not produce any appreciable changes, but during the second week the amount of intoxication from the same dose of alcohol was definitely increased. In the third and fourth weeks coma and intoxication, lasting from one to two hours, followed the injection of 1.5 c.c. of alcohol. In animals with 50 per cent fat and 0.1 per cent glycogen in the livers this dose usually proved fatal. Change from a fat to carbohydrate diet gradually restored the excessively fat livers to normal within a week. The tolerance to alcohol also improved and returned to normal at the same time.

It is of course true that tissues other than the liver are altered by the same measures that change the chemical composition of the liver. With the methods we have employed the changes in the liver are usually more than 10 times as great as the corresponding changes in other tissues, such as in the muscles or kidneys. In other animals after previous injury to the liver by toxic agents or by surgical measures, these other tissues are not sufficiently involved to produce detectable chemical changes, and the reaction to toxic agents again corresponds to the condition of the liver. We therefore feel justified in attributing the altered susceptibility to toxic agents which we have observed to alterations produced in the chemical composition and histologic appearance of the liver.

We have called attention to the fact that animals dying from extensive hepatic injury, regardless of the methods by which it is produced, do not show the typical symptoms or chemical changes that are found following complete

removal of the liver. The detoxicating function of the liver appears to be altered by changes in the organ so that its susceptibility to toxic agents is increased. Under most circumstances we feel that increased susceptibility to toxic agents is responsible for the symptoms shown, and that usually the animal succumbs before the entire function of the liver is lost. At least part of the toxic substances may be of metabolic origin and are somewhat related to the autolytic disintegration of injured hepatic tissue. These observations seem particularly true in animals with hepatic lesions, which do not appear to be very detrimental to the animal under ordinary conditions but which cause the animal to fail rapidly following surgical intervention that would be of no consequence to normal animals. Following operation, these animals are markedly lacking in resistance and extensive degenerative changes rapidly occur in the injured liver. Preoperative diets rich in carbohydrate and intravenous injection of glucose both before and after operation have enabled animals to recover under circumstances that would be fatal without the administration of carbohydrate.

Summary

Many of the functions of the liver may be completely performed by only a small portion of that organ. Extensive injury to the liver may show little influence on such functions as the excretion of bile, regulation of blood sugar, formation of urea, deaminization of amino acids, and so forth. Certain other functions of the liver appear to be more easily influenced by induced pathologic changes. The ability of the liver to form bile salts is easily impaired, but since the liver also destroys and excretes bile salts, no simple test involving bile salts seems capable of indicating the functional capacity of the liver. However, if due regard is taken of the circumstances, the finding of bile salts in the blood of jaundiced animals indicates that the condition of the liver is otherwise good. The disappearance of bile salts from the blood under these conditions indicates improvement as a result of relief from obstruction, or regression as a result of pathologic changes in the liver.

The detoxicating function of the liver also seems to be impaired easily. The systemic effects of several toxic agents are often roughly proportional to the extent of the abnormal chemical and histologic changes in the liver at the time of administration of the toxic agent. The changes that accompany a diet rich in carbohydrate seem to increase the resistance to some toxic agents, and the depletion of the glycogen content of the liver by fat diets or other means decreases the resistance; this can be illustrated with the administration of alcohol in doses which are almost without effect on animals fed carbohydrate but which are fatal to animals fed excessive fat. The alterations in susceptibility appear to be related to the glycogen content of the liver. Measures directed toward increasing the glycogen content of the liver appear to be of value in reducing the systemic effects of certain toxins, and they also appear to prevent further injury to the liver.

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CASE REPORT

PANCREATIC LITHIASIS *

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It is perhaps too generally accepted that pancreatic lithiasis is a rare condition. The relative paucity of reported cases is the basis for this assumption. Graef observed calculi in the pancreas for the first time in 1664. In 1932 Ackman and Ross [24] reported a case which, they stated, brought the total number up to 108.

It may safely be stated that the condition either is in reality so rare that few of us are privileged to see a case or that it presents difficulties of diagnosis that have prevented its more frequent recognition. In favor of the latter supposition is the fact that most of the earlier cases were discovered at necropsy, that later the diagnosis, if made, was usually based upon the findings at surgical exploration, and that it is only in the last two decades that reliable diagnostic help has been obtainable from the roentgen-ray.

The clinical symptoms are notoriously unreliable. The condition may be asymptomatic; there may be only mild digestive symptoms; there may be symptoms not readily referable to the digestive system; or there may be severe, persistent or intermittent epigastric pain. The roentgenologic finding of radiopaque areas suggestive of calculus in the upper abdomen may not solve the difficulty since even when these are not confused with renal or biliary calculi they may readily be interpreted as calcified retroperitoneal glands. It seems probable, nevertheless, that if in cases with mild or severe gastrointestinal symptoms due consideration be given to the possible presence of pancreatic calculi and advantage taken of all modern methods of diagnosis many more cases would be diagnosed.

The relief of many cases of pancreatic lithiasis in recent years by surgical operation and the fact that the untreated condition is often fatal, lend point to an attempt to present in tabular form a summary of the symptoms and findings in 22 of the more recent and carefully studied cases from the literature, and to the report of a case personally observed. The earlier reported cases include symptomatic data difficult to evaluate and are without laboratory or roentgenologic reports; they are therefore not included.

It is realized that the data on the cases in the foregoing table are incomplete but it is thought that all important points in the available abstracts have been included. Of the 22 cases listed, only six were in women. The youngest patient was 20 years old and the oldest 73 years of age. The most common subjective symptom was epigastric pain which often radiated to the back or shoulders. In its site or character there was nothing distinctive. Jaundice was present in some cases, but usually late, and was of no dependable diagnostic significance. Glyco-

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TABLE I

Sex	Age	Reported by	Chief Abdominal Symptoms	Other Symptoms	Roentgen-Ray	Operation
F.	24	Friedrich and Hoesch [3]	Epigastric pain radiating to left shoulder. Palpable epigastric tumor and marked loss of weight.	Presence of jaundice, glycosuria, and gall stones not stated.	Positive	Yes, for pancreatic cyst. Stones, found but not removed. Recovered.
M.	42	Mraz [4]	Pain in epigastrium, especially on left side. Fatty stools.	Presence of jaundice not stated. No glycosuria.	Not stated	Yes. Stones (45) removed. Recovered.
M.	46	Orth [5]	Pain in epigastrium, radiating to back. Frequent vomiting and diarrhea.	Presence of jaundice not stated. No glycosuria.	Positive	Yes. One large stone removed. Recovered.
M.	Not known	Meyer [6]	Sense of pressure in epigastrium. No pain. Fatty stools.	Presence of jaundice and glycosuria not stated.	Positive	Yes. One large stone removed. Recovered.
M.	37	Irsigler [7]	Epigastric pain radiating to left shoulder. Loss of weight. Acute attack simulating ruptured gastric ulcer requiring immediate operation. In shock.	Not stated. Gall bladder normal.	Not stated	Yes. Several stones. Died.
M.	33	d'Antona [8]	Intermittent diarrhea and undigested food remnants. Fatty stools.	Urine positive for sugar. Developed cardiac disease and died suddenly.	Not reported	No. Autopsy showed numerous stones in pancreatic duct and pancreatic parenchyma transformed into lipomatous tissue.
M.	51	Schöndube [9]	Symptoms of cirrhosis of liver and fatty stools. Diminution of pancreatic ferments.	Glycosuria present.	Positive	No. Autopsy confirmed diagnosis. No gall stones.

TABLE I (*Continued*)

Sex	Age	Reported by	Chief Abdominal Symptoms	Other Symptoms	Roentgen-Ray	Operation
F.	64	Perman [10]	Attacks of epigastric pain. Fatty feces. Jaundice, late.	No glycosuria.	Positive	Yes. At first operation gall stones were removed and at second pancreatic stones were removed. Patient died. Autopsy revealed another stone in pancreatic duct and carcinoma in head of pancreas, a metastasis from carcinoma of liver.
M.	67	Perman [10]	Attacks of severe epigastric pain. Intermittent diarrhea with grayish fetid stools.	Glycosuria present. Jaundice developed after operation.	Positive	Yes. Several stones removed. Patient died. Autopsy revealed sclerotic changes of pancreas but no more calculi.
M.	67	Öhnell [11]	Loose, gray, offensive, frequent stools for 30 years. Epigastric pain radiating to right shoulder with fatty stools last 6 months.	Glycosuria present. Jaundice late.	Positive	Yes. Several stones removed. Temporary relief of symptoms. Symptoms returned early and patient died. Autopsy revealed another stone and scirrhous carcinoma.
M.	45	Wolf and Tietze [12]	Diarrhea and loss of weight. Fatty stools. Slight abdominal pain just prior to passage of feces.	Blood sugar normal. Glucose tolerance slightly diminished.	Positive	Yes. Six stones removed. Patient recovered.
M.	46	Zukschwerdt [13]	Colicky abdominal pain for 8 years. After a blow on epigastrium he had severe epigastric pain and vomited blood.	Blood sugar 140 mg. Gallbladder operation 8 years previously. No stones. Tumor palpated at this time to right of median line but not investigated.	Positive for cyst of pancreas with numerous stones.	No. Patient refused operation. Case not confirmed by operation or autopsy but believed confirmed by presence of mass at exploratory operation and subsequent roentgen-ray.

TABLE I (*Continued*)

Sex	Age	Reported by	Chief Abdominal Symptoms	Other Symptoms	Roentgen-Ray	Operation
F.	20	Choy and Oh[14]	None mentioned.	Urinary retention, dyspnea, edema of legs, and "indigestion."	Not stated.	No. Died one month after admission. Autopsy confirmed nephritis. Also numerous pancreatic calculi. Stones consisted of calcium carbonate.
M.	56	Quénu [15]	Severe hematemesis and melena.	None stated.	Positive. At autopsy pancreas roentgen-rayed again and showed same shadows.	No. Patient died before operation was attempted. Autopsy showed stones of calcium carbonate with traces of phosphates. Source of hemorrhage could not be found.
M.	53	Fiessinger and Olivier [16]	Typical symptoms of cirrhosis of liver.	None stated. All symptoms over-shadowed by those of advanced cirrhosis of liver.	Not stated.	No. Autopsy showed marked cirrhosis of liver and pancreas and numerous stones in pancreas.
M.	Not stated	Soupault [17]	Pain in epigastrium, recurrent, with vomiting and slight fever. Tumor in epigastrium, soft and slightly painful.	After second operation developed high blood sugar, requiring diet and insulin.	First picture indicated cyst of pancreas. Another after second operation showed a chain of stones in duct of Wirsung.	Yes. First operation cyst drained. At second operation two stones found. At third operation several stones removed. Died 36 hours after last operation, from embolus. Autopsy showed additional stones in duct of Wirsung.
F.	35	Dillon [18]	None	Had diabetes 3½ years prior to death. Later developed pulmonary tuberculosis which caused death.	Not stated.	No. Autopsy showed numerous stones plugging the ducts with atrophy of tail of pancreas.

TABLE I (*Continued*)

TABLE I (*Continued*)

Sex	Age	Reported by	Chief Abdominal Symptoms	Other Symptoms	Roentgen-Ray	Operation
M.	56	Graham Hodgson [19]	Substernal pain radiating to back for 6 months. Two days before examination, severe vomiting.	None	Positive.	Yes. Pancreatic stone found. No further details given.
F.	73	Collins [20]	Severe intermittent epigastric pain radiating to back and left side of abdomen. Tenderness in epigastrium more marked on left side.	No glycosuria or jaundice.	Positive.	Yes. Single stone removed from tail of pancreas and, also, numerous gall stones removed. Died three days later.
M.	72	Vallery-Radot, Miget, and Gauthier-Villars [21]	Mild attacks epigastric pain and pain in right iliac fossa for 2 years. Intermittent diarrhea, anorexia, and marked loss of weight last 2 months. Abdominal pain more continuous but never severe. Vomited blood once. Fatty stools containing blood.	No glycosuria.	Not stated.	No. Autopsy showed carcinoma of liver with cirrhosis. Also multiple stones of pancreas with fatty degeneration of parenchyma of pancreas.
F.	58	Billaudet [22]	Epigastric pain intermittently for many years radiating to lower border liver and right shoulder accompanied by nausea. Last 8 years pain more continuous but less severe and no radiation. Stools normal.	No glycosuria or jaundice.	Positive. Picture of gall stones and pancreatic stone: the latter more dense.	Yes. One stone in pancreas removed. Also gall-bladder containing several stones, removed. Pancreatic stone consisted of calcium carbonate and phosphate and some magnesium phosphate.
M.	45	Quénu [23]	Attacks of epigastric pain radiating to back and becoming more frequent and severe. Loss of weight moderate.	None stated.	Positive after operation.	Yes. Large mass in head of pancreas considered carcinoma or chronic pancreatitis. Subsequent roentgenograms showed pancreatic stones. Symptoms became less severe. No operation attempted.

suria was noted in a minority of the cases. The examination of the abdomen in these patients was usually negative. In acute attacks, however, moderate rigidity was usually noted. Occasionally, but seldom, an upper abdominal mass was felt.

These symptoms and physical findings must be interpreted with due regard to the fact that in pancreatic lithiasis there is frequently an associated cholelithiasis, and that cirrhosis of the liver and pancreatic cyst are likewise often found present. There is very little speculative comment in the reports of the cases summarized

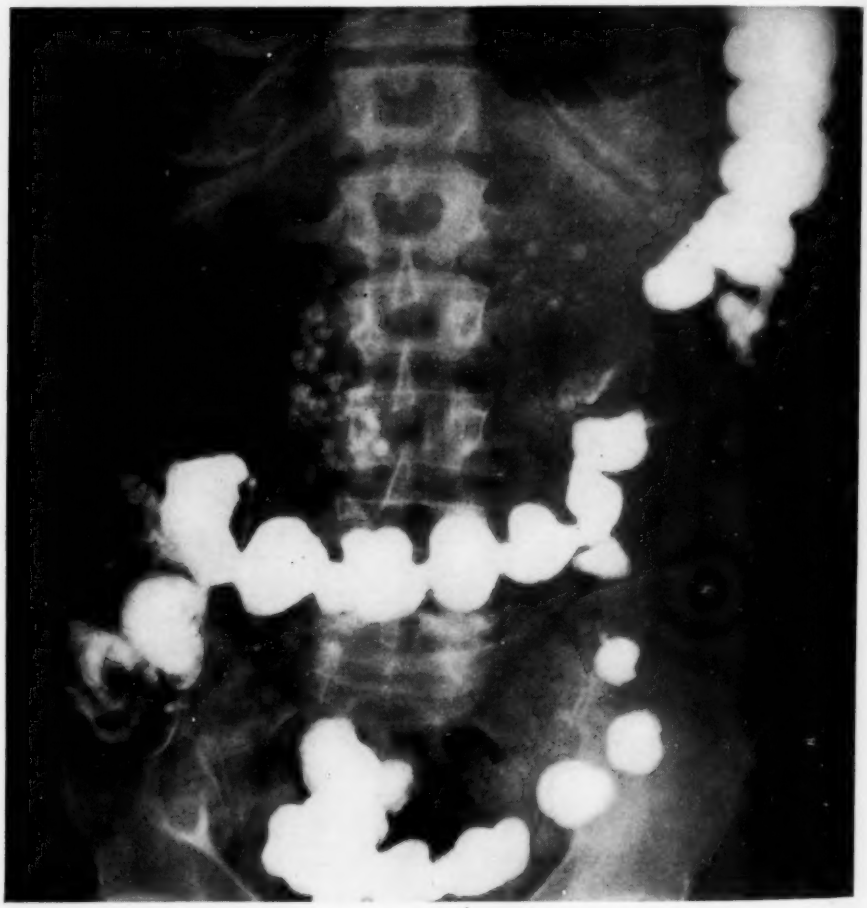

FIG. 1. Film after barium enema showing numerous dense shadows across entire epigastrium.

above as to the nature of these relationships except for the reasonable supposition that blockage of the pancreatic ducts by stones may lead to the formation of pancreatic cysts.

Such laboratory studies as have been reported have not been of great diagnostic help. Leukocytosis was encountered in only a few cases. Studies of the pancreatic juice contributed nothing of value. The presence of fatty stools, however, was frequently observed and might be considered suggestive. Chemical

analysis of the calculous material was reported in only a few instances; the results showed the presence of calcium carbonate with or without calcium phosphate and magnesium phosphate.

The greatest diagnostic help in these cases has been derived from roentgenography. The pancreatic stones cast shadows which are usually, according to the reports, denser than those which may be produced by gall stones. The interpretation of the roentgen findings presents some difficulties. Gall stones

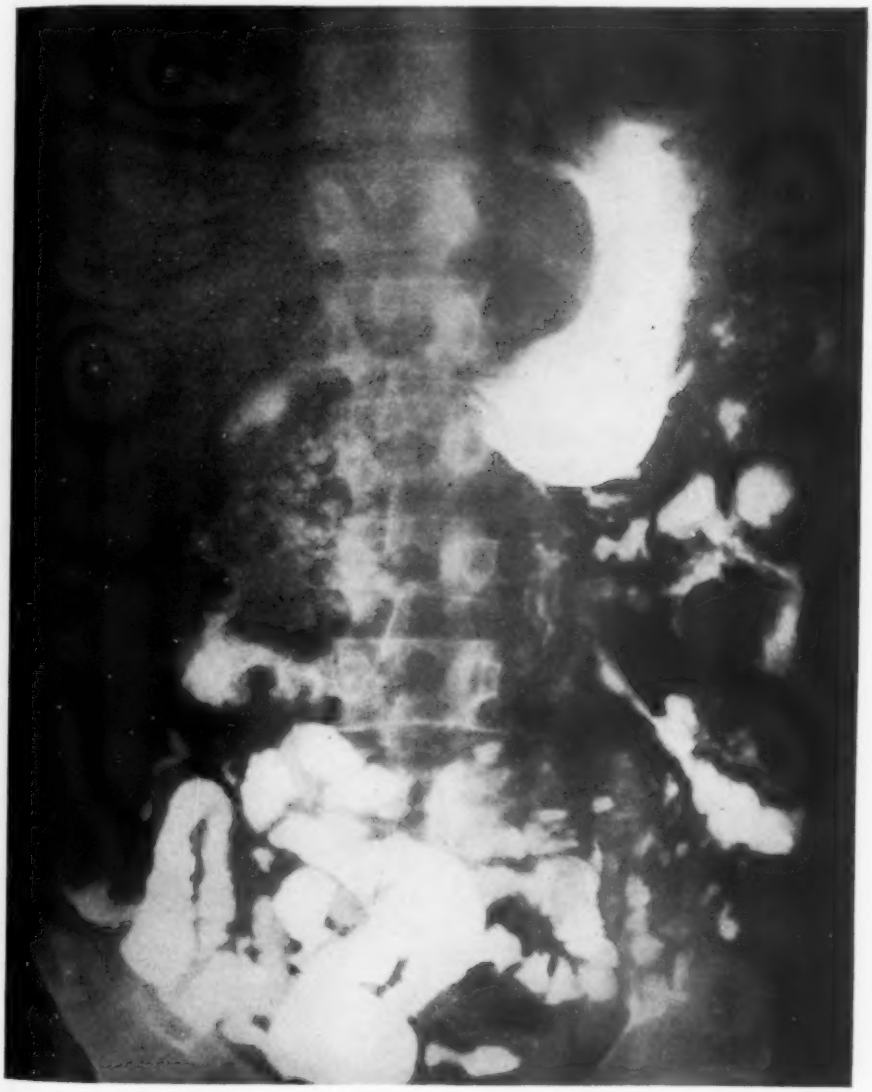

FIG. 2. Gastrointestinal series showing deformed and enlarged duodenal arc with numerous opaque densities in the epigastric region.

and renal calculi can usually be excluded by pyelograms and cholecystograms. The differentiation from calcified retroperitoneal or mesenteric glands, and from calcifications in the abdominal aorta or in abdominal aneurysms, may not give such definite results. The localization of the site of the calculus by fluoroscopy and films from lateral and oblique angles may rule out aortic involvement. Preceding the gastrointestinal series a swallow or two of barium viewed under the fluoroscope in oblique or lateral position may determine whether the shadow is in front of, or in rear of the bowel. Mention is made of the value of the gastro-

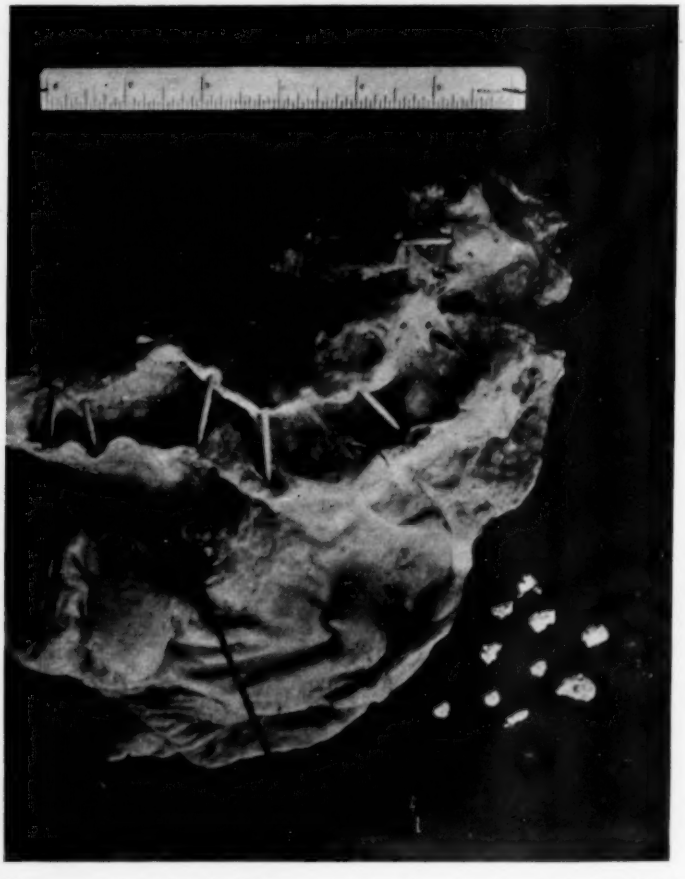

FIG. 3. Pancreas, stomach and duodenum removed en masse. Pointer indicates fistulous tract between pancreas and greater curvature of the stomach. A few of the calculi lying in dilated pancreatic duct are shown.

intestinal series in outlining distortion in the normal arc of the duodenum.

The following is an abstract of a case admitted to the Gastrointestinal Section of Letterman General Hospital, San Francisco, California. I believe this case is unusually interesting because it showed probably the most extensive involvement ever reported. The entire pancreas was involved and stones of all sizes were too numerous to count or even estimate. Stevens, in "The Practice of Medicine," (3d Edition, 1932) states: "The most common sequel to pancreatic lithiasis is

chronic interstitial pancreatitis which sometimes reaches an advanced grade. . . . The ducts of the gland are almost invariably dilated and occasionally true retention cysts are found. . . . Fistulous communications with stomach or duodenum have been reported. . . . Abscess and carcinoma are rare associations." This case

FIG. 4. Same specimen shown in figure 3. Note enormous size of pancreatic duct. Stones can be seen obstructing some of the smaller ducts.

is unusual in that it revealed the presence of all these complications except cysts and carcinoma.

CASE REPORT

The patient was a laboring man, 45 years old, a native of California. He formerly drank alcoholics excessively but only moderately in recent years. Arthritis

afflicted the left shoulder four years before. He has had numerous fractures as a result of injuries sustained in horse races. He denied all venereal diseases.

Present Illness. Symptoms referable to the gastrointestinal tract have been present for 10 or 12 years with apparent increasing severity. *Heartburn* for 10 years has appeared usually about 30 minutes after breakfast and again about 10 p.m. There is partial relief by the use of alkalies. *Pain* in the region of the umbilicus has appeared about one hour after meals. It has usually lasted about 30 minutes and has

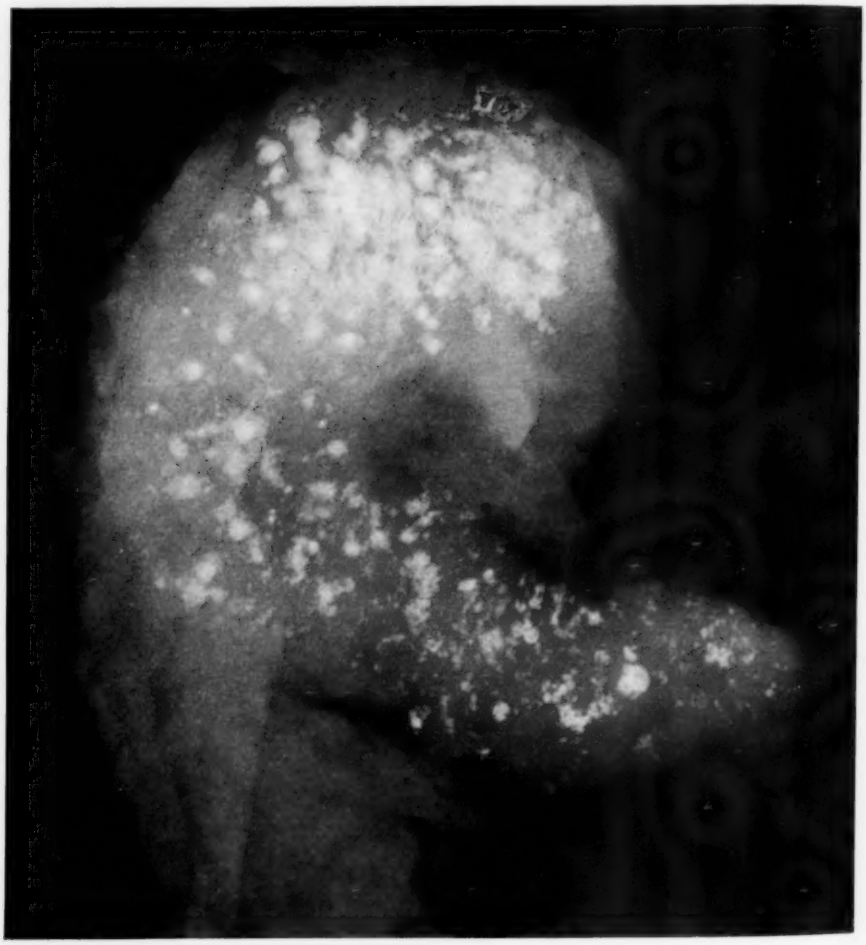

FIG. 5. Roentgen-ray of pancreas, stomach and duodenum after removal en masse at autopsy showing innumerable calculi involving the entire pancreas.

been rather severe, subsiding later to an almost continuous dull ache in the epigastric area. *Nausea* has been present frequently but *vomiting* has been rare. *Gaseous distention and eructation* have been present continuously. *Hematemesis* has been noted only once, about two years ago, when the vomitus contained about a teaspoonful of bright red blood. *Melena:* The patient believed he had passed tarry feces many times. The *appetite* has been poor for the last eight years.

The patient stated there have been frequent remissions when he was comfortable and able to work, only to be followed by a recurrence. There has been no history of jaundice or of clay colored feces, or of constipation or diarrhea. The teeth are in poor condition; many of them have been extracted. For years he has lived on a soft diet for this reason and also to prevent attacks of epigastric pain. On September 27, 1934, he developed severe pain in the epigastrium that "doubled him up." Because of these symptoms and the presence of muscular rigidity a tentative diagnosis of ruptured duodenal ulcer was made and he was admitted to the hospital.

On examination he was emaciated, weighing only 96 pounds. The skin was dry and warm; systolic blood pressure 110, diastolic 60. The abdomen was distended and there was marked tenderness over the umbilical region and in the left epigastrium with moderate rigidity. A mass could not be palpated.

Laboratory Findings: Repeated urinalyses were negative throughout. The blood count, repeated many times, was entirely normal except for the leukocyte count which varied from 7,200 (polymorphonuclear cells 76 per cent) to 19,400 (polymorphonuclear cells 91 per cent) just prior to the operation.

The blood Wassermann test was negative. On a prostatic smear many pus cells were seen.

Gastrointestinal roentgenograms showed that the arc of the duodenum was widened and that there were clusters of opaque bodies in this region extending to the left of the median line. The chest roentgenogram was negative. There was no air beneath the dome of the diaphragm.

The temperature ranged from normal to 101° F.

After obtaining the history, completing the physical examination and viewing the roentgenograms my impression was that he had either a peptic ulcer, or a carcinoma of the pancreas with calcified glands in the same region.

We could not proceed further with the study of the case due to the severe attacks of abdominal pain. The attacks by this time were very severe and would appear almost every hour. Food could no longer be tolerated. He was operated upon on October 8, 1934. The pancreas was markedly enlarged from head to tail and fluctuated. Pus was aspirated from which the colon bacillus was recovered. Crepitation was also noted in the pancreas. Drainage in two stages, with 48 hours intervening, was instituted.

The postoperative course was unfavorable and death occurred October 14, 1934, six days after operation. There had been no signs of generalized peritonitis nor was there apparent postoperative pneumonia or other lung involvement.

At autopsy, except in the area of the drainage tract leading from the skin wound down to the head of the pancreas, there was no increase of fluid in the peritoneal cavity. The serous surface was smooth and shining. Stomach, pancreas, and duodenum were removed together. The pancreas was very large and felt like the crop of a chicken, full of gravel and stones. The duodenum was negative. The stomach was negative except for an opening in the wall posteriorly on the greater curvature about 10 cm. from the pyloric ring. This opening was about 1 cm. in diameter with smooth, round edges that were not indurated. The stomach at this point was adherent to the pancreas by a plastic membrane that could be separated with little difficulty. There was pus in a little sac formed between the stomach and pancreas, suggesting a fistulous tract. The pancreas at this point was deeply pitted. Pus escaped through the fistulous tract from the pancreas on little pressure. The pancreas was opened from the ampulla. The opening of the main pancreatic duct was not evident to the eye on close inspection but just inside the opening the duct was dilated irregularly in places to as much as 3.5 cm. Much pus drained from this dilated duct and from the dilated branches leading into it. The wall of the main duct was thick and gray. There were no erosions or areas of softening. The pancreas as a whole, except for its resemblance to a "bag of gravel," was firm. The pus flowing from the dilated

ducts suggested an empyema rather than a suppurative pancreatitis. Many stones were lying in the dilated main duct, and others were lying in the dilated branches. These stones were as large as 1.3 by 0.9 by 0.7 cm. and were rough, with numerous projections, some suggesting coral formations. Several hundred stones were estimated to have been found. On analysis they were made up of calcium carbonate and calcium phosphate.

Microscopic examination of the pancreas shows evidence of progressive chronic pancreatitis of long standing, with many areas of calcium deposit. The arteries show marked endarteritis. The parenchyma appears to be much reduced. Superimposed is an acute suppuration involving not only the epithelium lining the ducts but also large areas of the gland tissue. The weight of the pancreas was not obtained as the stomach, duodenum, and pancreas were preserved en masse.

Summary

A case of pancreatic lithiasis is reported. Several hundred calculi involving the entire parenchyma as well as the ducts were found at necropsy.

Most of the usual, as well as the unusual, sequelae from pancreatic calculi involving the pancreas and adjacent organs, as reported by other observers, were noted.

Subjective symptoms, physical examination, and laboratory findings, are so variable and unreliable that they afford little aid in differentiating this condition from the more common disorders encountered in the upper abdomen.

Greater accuracy in diagnosis will result if pancreatic lithiasis be given proper consideration in the study of any patient complaining of acute or chronic abdominal distress. Careful study of roentgenograms will undoubtedly result in more frequent recognition of this condition.

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EDITORIAL

POSTURE AND BLOOD PRESSURE

THE physiologic responses of the circulatory system to changes in posture were first studied in animals by Hill and Barnard [1] in 1897. They found, by placing a dog in the vertical position, feet down, and cutting the cervical portion of the spinal cord, that the pressure in the aorta dropped to zero and most of the blood was collected in the splanchnic region. By squeezing the abdomen the aortic pressure returned to normal. Hill and Barnard also demonstrated that if rabbits raised in a hutch were placed in a vertical position, feet down, the animals would die in a very short time unless a tight abdominal binder was applied. The drop in blood pressure with change to the vertical position was attributed to a deficient vasomotor tone, associated with lack of tone of the abdominal wall.

In man, as early as 1905 Crampton [2, 3] studied and established the normal changes in blood pressure and pulse rate with change in posture. He considered that the alterations in blood pressure and pulse rate which occurred with change from the horizontal position to the vertical one were a measure of vasomotor tone as related to the splanchnic vessels. He developed an ingenious statistical arrangement for evaluating bodily fitness in terms of rise in blood pressure and drop in pulse rate and vice versa. This test was often applied to determine the physical fitness of athletes.

This work was seemingly overlooked for a time, with but an isolated worker here and there studying the effect of change in posture on blood pressure and pulse rate. Mortensen,[4] studying healthy young women, attributed the rise in systolic blood pressure not to vasomotor tone but to myocardial response to the effects of gravity and to muscular activity coincident with change of position. Likewise, Turner [5] studied the abnormal response of blood pressure to change in posture in apparently normal persons. He felt that, because of excessive loss of circulatory minute volume, anemia of the brain occurred and that this caused symptoms of dizziness and fainting on prolonged standing. An abnormal fall in systolic pressure alone was found most frequently in cases of myocardial degeneration. An abnormal fall in diastolic pressure alone was considered indicative of deficient vaso-

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motor tone, uncompensated by efficient abdominal and thoracic muscular action. This would result in congestion of the splanchnic circulation even though the myocardium were functionally intact.

In 1925, a new interest in the subject was awakened by the description of the clinical entity, postural or orthostatic hypotension, by Bradbury and Eggleston.[6] The essential characteristics of the syndrome, according to these authors are: (1) a sharp drop in systolic and diastolic blood pressure with syncopal attacks on change of posture from the recumbent to the upright position; (2) no increase in the pulse rate with this drop in blood pressure; (3) anhydrosis, associated with intolerance to heat during the summer months; (4) a larger volume of urine excreted at night than in the daytime. A possible explanation, as given by Bradbury and Eggleston, was a deficiency or paralysis of the myoneural junctions. At this time no successful treatment was established. It was not until 1928 that a satisfactory treatment was discovered by Ghrist and Brown,[7] when it was shown that the oral administration of ephedrine sulphate would maintain the blood pressure when the subject was in the upright posture. These workers concluded that the essential disturbance in the disease was the lack of resistance in the splanchnic vessels to shifts in the blood mass and absent or diminished vagus regulation of the cardiac rate to changes in the blood pressure.

In contrast to the above stated hypotheses, a group of English workers have suggested that, since the predominant afferent impulses responsible for the production and control of postural tone are proprioceptive, and arise in the muscles of the extremities, the lower limbs play an important part in the mechanism of postural hypotension. MacWilliam[8] maintains that the increased fall in blood pressure and rise in pulse rate, with the change in position of the patient from the sitting to the standing position, are attributable to the position of the limbs. Otherwise, the trunk is in the vertical position under both conditions and therefore the effect cannot be attributable to the direct effect of gravity on the splanchnic region. However, Crampton has stated that the splanchnic circulation is kept within bounds by the support received from the flexed position of the sitting posture.

Henderson[9] has expressed the belief that there is another important factor in circulatory efficiency, which he calls the "venopressor mechanism." This factor chiefly determines the venous return to the right side of the heart. The venopressor mechanism consists of the mechanical effect of the general tonus of the bodily musculature, and more especially the tonus of the abdominal muscles and particularly of the diaphragm, as well as of the non-

[6] Bradbury, S., and Eggleston, C.: Postural hypotension; a report of three cases, Am. Heart Jr., 1925, i, 73–86.

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striated muscles of the alimentary canal which all exert an effect on the contents of the splanchnic veins.

Following extensive anterior rhizotomy, with complete resection of the pre-ganglionic fibers that go to make up the splanchnic nerves, in patients with hypertension, two conditions are produced: (1) a denervation of the splanchnic vessels, and (2) relaxation of the abdominal wall. There is a rather striking similarity between these patients and the group with postural hypotension. The decrease in blood pressure is considerably greater when the subject is in the upright position than when he is recumbent. Occasionally, the decrease in blood pressure on standing is sufficient to produce syncope. This tendency is only temporary in most instances and may be remedied by the wearing of a tight abdominal binder. The level of blood pressure at which syncope occurs is generally much higher than in the patients with postural hypotension, but the latter group maintains a much lower level of blood pressure in the recumbent position. An interesting observation was made in one patient with an advanced, organic form of hypertension. Following section of all the intercostal nerves on both sides, no significant change in the blood pressure occurred with change to the upright position. The conclusion may be drawn that the relaxation of the intercostal and abdominal muscles alone was not sufficient to disturb the blood pressure in this instance; and that the vasomotor system plays the predominant rôle in the decrease of blood pressure in the upright position.

Up to the present, eighteen cases of postural or orthostatic hypotension have been reported, with almost as many theories for the etiology of the disease. There may be a phylogenetic basis for this failure in the support of blood pressure in the ascent of man from the four-legged animal to the upright one. Since the group as a whole contains individuals with certain inadequacies, it is probably a measure of fitness. The fact that epinephrine and ephedrine, drugs which act on the myoneural junctions, produce rises in blood pressure, suggests that these structures are functioning, in part at least. The sharp drop in blood pressure in the upright posture demonstrable in the cases of hypertension in which operative interruption of the splanchnic innervation has been carried out is strong evidence that the vasomotor mechanism plays a definite rôle in all instances of postural hypotension.

G. R.

BOOK REVIEWS

Diseases of the Nervous System. By W. Russell Brain, M.A., F.R.C.P. (London). xvi + 899 pages; 15.5 × 22.5 cm. Oxford University Press, London. 1933.

In recent years the field of neurology has been intensively cultivated by many who were not primarily neurologists: the bacteriological studies of the various forms of encephalomyelitis; the surgical attack upon tumors of the brain and cord, upon certain diseases of the peripheral nerves and upon intractable pain; and the physiological and clinical studies of the interrelationship of the autonomic system and of the endocrines with bodily structure and visceral function; all these and other developments have greatly added to the scope of neurology and altered our conception of the relative importance of the various neurological disorders.

Dr. Brain has achieved in this volume an exceptionally well balanced and lucid account of the present status of clinical neurology. This is in large part due to his skillful arrangement of the material. After an introductory section of 116 pages on disorders of function in the light of anatomy and physiology, the diseases of the nervous system are discussed in seventeen further sections. They are grouped according to practical clinical relationships rather than forced into apparently logical subdivisions. The grouping is sometimes anatomical, as in the section on the cranial nerves, sometimes etiological as in the section on the infections of the nervous system and sometimes functional as in the section entitled "Hydrocephalus and Intracranial Tumor." Sections frequently are opened by a brief chapter on the anatomical and physiological data necessary to an understanding of the diseases later described. Frequently also a chapter will be devoted to topical discussion as, for examples, those devoted to Headache, to Compression of the Spinal Cord, and to the Late Effects of Head Injuries. These features in the arrangement of the material add greatly to the practical usefulness of the volume to the clinician.

The author has succeeded in including a brief but usually adequate discussion of even the most recently differentiated neurologic syndromes or diseases and has drawn freely on the American and Continental literature of both neurology and internal medicine. The references given are well selected.

The point of view is conservative, at times a little dogmatic perhaps because of the requirements of brevity. The book is unusually readable because of its clear, easy style. It appears to be a very desirable textbook for students and it will prove of equal or greater value to the internist for quick reference and also as a means of bringing him abreast of the advances in modern neurology.

M. C. P.

Diabetes Mellitus and Obesity. By Garfield G. Duncan, M.D. xii + 227 pages; 14 × 20.5 cm. Lea and Febiger, Philadelphia. 1935. Price, $2.75.

In this small volume an attempt has been made to give the general practitioner and the student a working knowledge of the two metabolic diseases with which he will most commonly have to deal, diabetes mellitus and obesity. The subject matter is condensed, the stress is laid on practical methods of treatment. The greater portion of the work is devoted, rightfully, to diabetes and to its complications. The subject of obesity is only briefly considered. An appendix contains useful food tables and weight scales.

Chapter 8 contains an excellent outline of the procedures followed with diabetic patients in the Metabolic Clinic, "B" service and ward at the Pennsylvania Hospital. It will be of interest and of value to all those concerned in organizing adequate treatment of such cases.

This clearly written short monograph will be of value to many physicians who have wanted something more than a diet manual and something briefer than a long treatise.

J. S. E.

Hospital Organization and Management. By MALCOLM T. MACEACHERN, M.D., C.M., D.Sc. 944 pages; 17 × 25 cm. Physicians' Record Co., Chicago, Ill. 1935. Price, $7.50.

This volume is extraordinary in its completeness and will undoubtedly be of great value to hospital administrators as a reference book. Its general usefulness is widened also by the fact that it deals not only with purely administrative hospital problems but also discusses at great length the various problems peculiar to each professional department. The book contains a great deal of material that should be of as much interest to the physician in chief, director of nurses, dietitian, chief engineer, and others as to the administrators themselves.

Dr. MacEachern of course is well known in the field of hospital administration and has put the results of many years of study into his book. The arrangement of material is extremely concise in that each step in planning a new organization is taken up in the logical order, from the organization of the governing body to the actual opening and dedication of a functioning hospital. One of the most interesting characteristics of the book is that the material presented is such that it is made applicable to all types and sizes of institutions with no neglect of detail which is peculiar to one or another sort of hospital.

M. L. S.

Fifty Years of Medicine and Surgery. By FRANKLIN H. MARTIN. 449 pages; 14 × 21.5 cm. The Surgical Publishing Company of Chicago, Chicago, Ill. 1934.

This volume, which was issued a very short time before the author's death, contains a very readable account of his interesting career. Dr. Martin was a man of strong personality who often bent men and events to conform with his will. It is still early to appraise his achievements as an Editor and in connection with the development of the American College of Surgeons and the rôle it has played in elevating the standards of surgery and of hospitals in this country. There is no doubt, however, that this book will always prove an interesting document in the study of the medical history of a period during which its author was a living force.

M. C. P.

Principles and Practice of Physical Diagnosis. By PAUL MARTINI; translated from the Italian by Robert S. Loeb. 213 pages. J. B. Lippincott Co., Philadelphia. 1935. Price, $2.00.

Dr. Martini's textbook is pocket size, brief and concise. It contains a summary of the principles underlying physical examination. It gives the essential findings in the common pathological conditions of the chest and abdomen. The accessory aids in diagnosis, roentgenology and electrocardiography, are brought in from time to time in order to give the reader a more complete grasp of the subject. At times there seems to be a tendency to over simplification of points that are in reality obscure. It is essentially an undergraduate textbook.

T. C. W.

COLLEGE NEWS NOTES

American Board for the Certification of Internists

By resolution adopted by the Board of Regents of the American College of Physicians on April 30, 1935, and by resolution adopted by the Section on the Practice of Medicine of the American Medical Association on June 14, 1935, a committee consisting of nine members, six from the American College of Physicians and three from the Section on Medicine of the American Medical Association, will meet at Philadelphia, December 14, to discuss ways and means whereby an examining board, comparable to such boards existing in certain specialties, may be set up for the purpose of certification of specialists in Internal Medicine. The personnel of the Committee, as appointed by the American College of Physicians and by the Section on Medicine of the American Medical Association, is as follows:

Walter L. Bierring (A.M.A.), Chairman of the joint Committee
David P. Barr (A.C.P.)
Reginald Fitz (A.M.A.)
Ernest E. Irons (A.M.A.)
Jonathan C. Meakins (A.C.P.)
William S. Middleton (A.C.P.)
John H. Musser (A.C.P.)
O. H. Perry Pepper (A.C.P.)
G. Gill Richards (A.C.P.)

The expenses of the Board will be underwritten by the American College of Physicians until met by fees of candidates.

The Board is not concerned with the problem of the use to which its certification may be put by the American College of Physicians in selection of Associates or Fellows.

The Board's first responsibilities will consist of determining upon the plan for examination, the character of examination and how and when the examinations shall be given.

Gifts to the College Library

Acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Dr. Miles J. Breuer (Fellow), Lincoln, Nebr.—1 reprint;
Dr. Ronald L. Hamilton (Fellow), Sayre, Pa.—4 reprints;
Dr. Arthur A. Herold (Fellow), Shreveport, La.—1 reprint;
Dr. Martin J. Synnott (Fellow), New York, N. Y.—1 reprint;
Dr. Frederick H. Foucar (Associate), Washington, D. C.—1 reprint;
Dr. William G. Leaman, Jr. (Associate), Philadelphia, Pa.—4 reprints;
Dr. W. K. Purks (Associate), Vicksburg, Miss.—7 reprints;
Dr. Frank A. Trump (Associate), Ottawa, Kan.—2 reprints.

Dr. Horace P. Marvin (Associate), Captain, Medical Corps, U. S. Army, has been transferred from duty at the Station Hospital, Schofield Barracks, Hawaii, to Fort Bragg, N. C. He is at present pursuing postgraduate work in Internal Medicine at the University of Minnesota (Mayo Foundation), and will report to Fort Bragg in February, 1936.

Dr. William Nimeh (Fellow), Mexico City, Mexico, was lately elected a Fellow of the Society for the Advancement of Gastroenterology, a member of its Council and foreign collaborator on its Review for Mexico.

Dr. Edward G. Huber (Fellow), Colonel, Medical Corps, U. S. Army, was retired from active service on August 31. He has been appointed an Instructor in the School of Public Health of Harvard University, Department of Preventive Medicine and Epidemiology.

Twenty-eight Fellows and four Associates participated either as speakers or clinicians on the program of the Eighth Annual Graduate Fortnight of the New York Academy of Medicine, October 21 to November 2.

The annual Graduate Fortnight is conducted on some subject of outstanding importance in the practice of medicine or surgery, and consists of meetings at the Academy, coördinated clinics in selected hospitals and a large scientific exhibit. This year the program was devoted to diseases of the respiratory tract.

Dr. William Henry Walsh (Fellow), Hospital Consultant of Chicago, recently conducted a study of the needs and plans for a new hospital to be erected through PWA funds to replace the old Erlanger Hospital in Chattanooga, Tenn.

The Eighth District Medical Society of North Carolina, embracing ten counties, held a recent meeting at Greensboro, N. C., the meeting being largely attended. One of the outstanding features of the program was an address by Dr. E. J. G. Beardsley (Fellow), Associate Professor of Medicine at Jefferson Medical College of Philadelphia and Governor of the American College of Physicians for eastern Pennsylvania. His subject was "A Physician's Opportunities and Responsibilities." Dr. D. W. Holt (Associate), Greensboro, President of the Society, presided. Dr. Roy C. Mitchell (Fellow), Mount Airy, N. C., is the District Governor of the Society. Dr. Wingate M. Johnson (Fellow), Winston-Salem, N. C., presented an interesting paper on "Some Observations and Impressions about Influenza." "Asthma in Children" was another interesting paper presented by Dr. S. F. LeBauer (Associate), Greensboro. Dr. J. P. Leake (Fellow), Medical Director of the Department of Epidemiology of the U. S. Public Health Service, presented a discussion on poliomyelitis and a résumé of the recent epidemic in that section.

Dr. Charles R. Drake (Fellow) was recently elected President of the Minneapolis (Minn.) Board of Education.

Dr. John Richards Aurelius (Fellow), St. Paul, Minn., has been elected Vice-President of the Minnesota Radiological Society.

Dr. William Branch Porter (Fellow), Professor of Medicine at the Medical College of Virginia, Richmond, spent a part of the past summer in San Juan, P. R., pursuing investigative work on the blood flow in cases of anemia, his experiments being conducted at the University Hospital of the School of Tropical Medicine, the Municipal Hospital and Mimiya Clinic.

Dr. Joseph A. Mendelson (Associate), Major, Medical Corps, U. S. Army, has been elected President of the newly organized Tientsin Medical Society in Tientsin, China.

Dr. Robert U. Patterson (Fellow), Major General, Medical Corps, U. S. Army, retired September 1 as Surgeon General of the U. S. Army to become Dean of the University of Oklahoma School of Medicine and Superintendent of the University Hospital.

During the World War, in recognition of his services abroad, Dr. Patterson received the Distinguished Service Medal and other citations for "gallantry in action."

Dr. George W. Covey (Fellow), Lincoln, Nebr., is President-Elect of the Nebraska State Medical Association. Dr. George L. Pinney (Fellow), Hastings, Nebr., is a Vice-President and Dr. Homer Davis (Fellow), Genoa, Nebr., is a Councillor.

Dr. John N. Simpson (Fellow), Dean of the Medical Faculty of the West Virginia University School of Medicine since 1902, recently retired with the title of Dean Emeritus. Dr. Edward J. Van Liere (Fellow), Professor and Head of the Department of Physiology, has been appointed Acting Dean.

Dr. William Lloyd Sheep (Fellow), Lieutenant Colonel, Medical Corps, U. S. Army, has been appointed Chief of the Medical Service and Commanding Officer of the Army and Navy General Hospital, Hot Springs National Park, Ark.

Dr. Hugh A. Beam (Fellow), Moline, Ill., is Medical Director of the Rock Island County Tuberculosis Sanatorium, this appointment having begun on August 1.

Dr. Albert D. Foster (Fellow), of the U. S. Public Health Service, has been transferred from the Medical Directorship at the U. S. Marine Hospital at Chelsea, Mass., to a corresponding position at the U. S. Marine Hospital, Portland, Maine.

Dr. Martha Tracy (Fellow), Dean of the Woman's Medical College of Pennsylvania, Philadelphia, has been granted a year's leave of absence. Dr. Henry D. Jump, Philadelphia, will be the Acting Dean during her absence.

Drs. Henry L. Bockus, Russell S. Boles and B. B. Vincent Lyon, of Philadelphia; Max Einhorn, of New York City; Sara Jordan and Franklin W. White, of Boston; and William Gerry Morgan, of Washington, D. C., all Fellows of the College, were among those appointed by the Department of State of the United States Government as delegates from the United States to the First International Congress of Gastroenterology at Brussels, during the past August.

Dr. J. K. Williams Wood (Associate), Willow Grove, Pa., has been elected President of the Lehigh Valley Medical Association.

Dr. C. Howard Marcy (Fellow), Pittsburgh, Pa., is President of the Pennsylvania Tuberculosis Society, and also President of the Pittsburgh Academy of Medicine.

Dr. William S. Middleton (Fellow), for some years Professor of Medicine at the University of Wisconsin Medical School, has been appointed Dean, to succeed the late Dr. Charles R. Bardeen.

Drs. Richard A. Kern, T. Grier Miller and Charles C. Wolferth (Fellows), Philadelphia, have been promoted to professorships in clinical medicine, and Dr. Truman G. Schnabel (Fellow), Philadelphia, to Associate Professor of Medicine on the faculty of the University of Pennsylvania School of Medicine.

Dr. John T. Farrell, Jr. (Fellow), Philadelphia, has been appointed assistant professor of roentgenology and roentgenologist of the Department of Anatomy of the Jefferson Medical College of Philadelphia.

Dr. Walter L. Treadway (Fellow), Washington, D. C., is a member of the faculty appointed at George Washington University School of Medicine in connection with its new four-year integrated curriculum in public health teaching, to parallel its curriculum in mental health established three years ago under Dr. William A. White (Fellow), Washington, D. C.

Dr. George B. Eusterman (Fellow), Rochester, Minn., Dr. Walter Freeman (Fellow), Washington, D. C., Dr. Bernard Fantus (Fellow), Chicago, Ill., and Dr. Ernest E. Irons (Fellow), Chicago, Ill., were among the speakers selected by the Iowa State Medical Society for its graduate course on general therapeutics conducted in Davenport from September 13 to November 15.

Dr. Coy C. Carpenter (Fellow) has been appointed Assistant Dean of Wake Forest College of Medicine, Wake Forest, N. C. Dr. Carpenter has been Professor of Pathology at this institution for some time.

Dr. Enrique Koppisch (Associate), San Juan, P. R., is on a Rockefeller Foundation Fellowship at Basel, Switzerland, studying filtrable viruses.

Dr. Rafael Rodriguez-Molina (Associate), San Juan, P. R., is at the University of Chicago pursuing courses in hospital management and administration.

Dr. Max Pinner (Fellow) has recently resigned his position as Associate Director, in charge of the laboratories of the Desert Sanatorium, Tucson, Arizona, in order to accept the appointment by the New York State Department of Health as

Principal Diagnostic Pathologist to be in charge of the laboratories of the three New York State Tuberculosis Hospitals in Mount Morris, Ithaca and Oneonta. From November 1 on Dr. Pinner's headquarters will be at Oneonta until the Herman Biggs Memorial Hospital at Ithaca is completed.

State Meeting of Illinois Members of the College at Springfield

Members of the American College of Physicians of Illinois outside of Chicago held a very successful regional meeting on September 24 at Springfield. A brief medical program was presented in the late afternoon. A paper by Dr. Horace W. Soper and Dr. J. W. Thompson on "Combined Medical and Surgical Management of Gastric and Duodenal Ulcer; with Emphasis on the Management of Gastro-Duodenal Hemorrhage" was read by Dr. Thompson. After conclusion of the discussion the members met at dinner.

Dr. Ernest B. Bradley, President-Elect, and his associate, Dr. Walter S. Wyatt of Lexington, Kentucky, were guests at the meeting and their presence was very much appreciated by the Fellows. Dr. Nathan S. Davis III of Chicago presented cordial greetings from the members of the College in Cook County. Major Eugene G. Remartz (Fellow), now stationed at Chanute Field, represented our membership in the military services.

The sentiment of the Fellows of the College as freely expressed at the close of the dinner was that the meeting had afforded them a pleasurable opportunity for closer acquaintance and that they were enthusiastically in favor of continuing such a regional meeting as an annual event.

Samuel E. Munson,
Governor for Southern Illinois

OBITUARY

DR. STEWART VERNON IRWIN

Dr. Stewart Vernon Irwin of Oakland, California, died suddenly in San Francisco on July 1, 1935. Death was due to coronary thrombosis. He had been advised to take a long rest from his professional duties and was about to carry out this advice, when the final attack came. Dr. Irwin was born in Oakland and received his early education in the San Francisco Bay region, graduating from the University of California, with the degree of B.S., in 1911. He attended Johns Hopkins University Medical School, receiving his degree of M.D. in 1915. During the next five years he served as assistant resident and resident physician at the Johns Hopkins Hospital.

In 1920 he came to Oakland, specializing in Internal Medicine. He became physician-in-chief of the Providence Hospital. Dr. Irwin served under Professor Llewllys Barker, while at the Johns Hopkins Hospital, and became imbued with a sympathetic interest in the psychic aspects of internal medicine, which interest he maintained successfully throughout his medical career. Somewhat reserved in personality, Stewart Irwin was a brilliant thinker and a sound diagnostician. He was elected to Fellowship in the American College of Physicians on December 20, 1931.

ERNEST H. FALCONER, M.D., F.A.C.P.,
San Francisco, Calif.